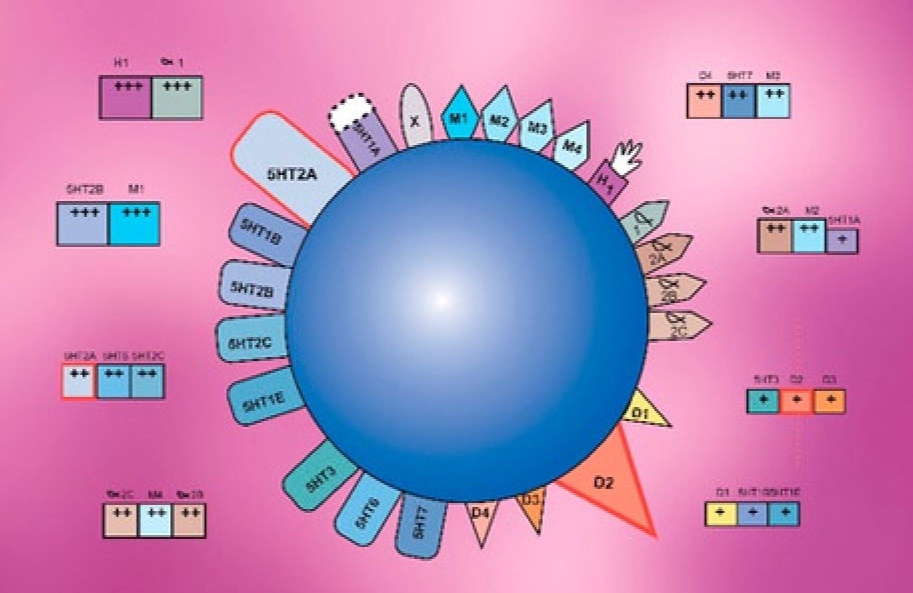
Stephen M. Stahl

Fourth Edition

Stahl's Essential Psychopharmacology

Neuroscientific Basis and Practical Applications



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Stahl's Essential Psychopharmacology

Neuroscientific Basis and Practical Application

Fourth Edition

With this fully revised Fourth Edition, Dr. Stahl returns to the essential roots of what it means to become a neurobiologically empowered psychopharmacologist, expertly guided in the selection and combination of treatments for individual patients in practice.

Embracing the unifying themes of "symptom endophenotypes," dimensions of psychopathology that cut across syndromes, and "symptoms and circuits," every aspect of the text has been updated to the frontiers of current knowledge, with the clarity of explanation and illustration that only Dr. Stahl can bring.

Integrating much of the basic neuroscience into the clinical chapters, and with major additions in the areas of psychosis, antipsychotics, antidepressants, impulsivity, compulsivity, and addiction, this is the single most readily readable source of information on disease and drug mechanisms.

This remains the essential text for all students and professionals in mental health seeking to understand and utilize current therapeutics, and to anticipate the future for novel medications.

Stahl's Essential Psychopharmacology

Neuroscientific Basis and Practical Application

Fourth Edition

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In memory of Daniel X. Freedman, mentor, colleague, and scientific father

To Cindy, Jennifer, and Victoria

Contents

Preface to the fourth edition

For this fourth edition of *Stahl's Essential Psychopharmacology* you will notice there is a new look and feel. With a new layout, displayed over two columns, and an increased page size we have eliminated redundancies across chapters, have added significant new material, and yet have decreased the overall size of the book.

Highlights of what has been added or changed since the 3rd edition include:

- Integrating much of the basic neurosciences into the clinical chapters, thus reducing the number of introductory chapters solely covering basic neurosciences.
- Major revision of the psychosis chapter, including much more detailed coverage of the neurocircuitry of schizophrenia, the role of glutamate, genomics, and neuroimaging.
- One of the most extensively revised chapters is on antipsychotics, which now has:
  - new discussion and illustrations on how the current atypical antipsychotics act upon serotonin, dopamine, and glutamate circuitry
  - new discussion of the roles of neurotransmitter receptors in the mechanisms of actions of some but not all atypical antipsychotics
    - $5HT_7$ receptors
    - $5HT_{2C}$ receptors
    - α_1-adrenergic receptors
  - completely revamped visuals for displaying the relative binding properties of 17 individual antipsychotics agents, based upon log binding data made qualitative and visual with novel graphics
  - reorganization of the known atypical antipsychotics as
    - the "pines" (peens)
    - the "dones"
    - two "pips"
    - and a "rip"
  - inclusion of several new antipsychotics
    - iloperidone (Fanapt)
    - asenapine (Saphris)
    - lurasidone (Latuda)
  - extensive coverage of switching from one antipsychotic to another
  - new ideas about using high dosing and polypharmacy for treatment resistance and violence
  - new antipsychotics in the pipeline
    - brexpiprazole
    - cariprazine
    - selective glycine reuptake inhibitors (SGRIs, e.g., bitopertin [RG1678], Org25935, SSR103800)
- The mood chapter has expanded coverage of stress, neurocircuitry, and genetics.
- The antidepressant and mood stabilizer chapters have:
  - new discussion and illustrations on circadian rhythms
  - discussion of the roles of neurotransmitter receptors in the mechanisms of actions of some antidepressants
    - melatonin receptors
    - $5HT_{1A}$ receptors
    - $5HT_{2C}$ receptors
    - $5HT_3$ receptors
    - $5HT_7$ receptors
    - NMDA glutamate receptors
  - inclusion of several new antidepressants
    - agomelatine (Valdoxan)
    - vilazodone (Viibryd)

    - vortioxetine (LuAA21004)
    - ketamine (rapid onset for treatment resistance)
- The anxiety chapter provides new coverage of the concepts of fear conditioning, fear extinction, and reconsolidation, with OCD moved to the impulsivity chapter.
- The pain chapter updates neuropathic pain states.
- The sleep/wake chapter provides expanded coverage of melatonin and new discussion of orexin pathways and orexin receptors, as well as new drugs targeting orexin receptors as antagonists, such as:
  - suvorexant/MK-6096
  - almorexant
  - SB-649868
- The ADHD chapter includes new discussion on how norepinephrine and dopamine tune pyramidal neurons in prefrontal cortex, and expanded discussion on new treatments such as:
  - guanfacine ER (Intuniv)
  - lisdexamfetamine (Vyvanse)
- The dementia chapter has been extensively revamped to emphasize the new diagnostic criteria for Alzheimer's disease, and the integration of biomarkers into diagnostic schemes including:
  - Alzheimer's diagnostics
    - CSF Aβ and tau levels
    - amyloid PET scans, FDG-PET scans, structural MRI scans
  - multiple new drugs in the pipeline targeting amyloid plaques, tangles, and tau
    - vaccines/immunotherapy (e.g., bapineuzumab, solenezumab, crenezumab), intravenous immunoglobulin
    - γ-secretase inhibitors (GSIs, e.g., semagacestat)
    - β-secretase inhibitors (e.g., LY2886721, SCH 1381252, CTS21666, others)
- The impulsivity–compulsivity and addiction chapter is another of the most extensively revised chapters in this fourth edition, significantly expanding the drug abuse chapter of the third edition to include now a large number of related "impulsive–compulsive" disorders that hypothetically share the same brain circuitry:
  - neurocircuitry of impulsivity and reward involving the ventral striatum
  - neurocircuitry of compulsivity and habits including drug addiction and behavioral addiction involving the dorsal striatum
  - "bottom-up" striatal drives and "top-down" inhibitory controls from the prefrontal cortex
  - update on the neurobiology and available treatments for the drug addictions (stimulants, nicotine, alcohol, opioids, hallucinogens, and others)
  - behavioral addictions
    - major new section on obesity, eating disorders, and food addiction, including the role of hypothalamic circuits and new treatments for obesity
    - lorcaserin (Belviq)
    - phentermine/topiramate ER (Qsymia)
    - bupropion/naltrexone (Contrave)
    - zonisamide/naltrexone
    - obsessive–compulsive and spectrum disorders
    - gambling, impulsive violence, mania, ADHD and many others

One of the major themes emphasized in this new edition is the notion of **symptom endophenotypes**, or dimensions of psychopathology that cut across numerous syndromes. This is seen perhaps most dramatically in the organization of numerous disorders of impulsivity/compulsivity, where impulsivity and/or compulsivity are present in many psychiatric conditions and thus "travel" trans-diagnostically without respecting the DSM (*Diagnostic and Statistical Manual*) of the American Psychiatric Association or the ICD (*International Classification of Diseases*). This is the future of psychiatry – the matching of symptom endophenotypes to hypothetically malfunctioning brain circuits, regulated by genes, the environment, and neurotransmitters. Hypothetically, inefficiency of information processing in these brain circuits creates symptom expression in various psychiatric disorders that can be changed with psychopharmacologic agents. Even the DSM recognizes this concept and calls it Research Domain Criteria (or RDoC). Thus, impulsivity and compulsivity can be seen as domains of psychopathology; other domains include mood, cognition, anxiety, motivation, and many more. Each chapter in this fourth edition discusses "symptoms

and circuits" and how to exploit domains of psychopathology both to become a neurobiologically empowered psychopharmacologist, and to select and combine treatments for individual patients in psychopharmacology practice.

What has not changed in this new edition is the **didactic style** of the first three editions. This text attempts to present the fundamentals of psychopharmacology in **simplified and readily readable form**. We emphasize current formulations of disease mechanisms and also drug mechanisms. As in previous editions, the text is not extensively referenced to original papers, but rather to textbooks and reviews and a few selected original papers, with only a limited reading list for each chapter, but preparing the reader to consult more sophisticated textbooks as well as the professional literature.

The organization of information continues to apply the principles of **programmed learning** for the reader, namely repetition and interaction, which has been shown to enhance retention. Therefore, it is suggested that novices first approach this text by going through it from beginning to end, reviewing only the color graphics and the legends for those graphics. Virtually everything covered in the text is also covered in the graphics and icons. Once having gone through all the color graphics in these chapters, it is recommended that the reader then go back to the beginning of the book, and read the entire text, reviewing the graphics at the same time. After the text has been read, the entire book can be rapidly reviewed again merely by referring to the various color graphics in the book. This mechanism of using the materials will create a certain amount of programmed learning by incorporating the elements of repetition, as well as interaction with visual learning through graphics. Hopefully, the visual concepts learned via graphics will reinforce abstract concepts learned from the written text, especially for those of you who are primarily "visual learners" (i.e., those who retain information better from visualizing concepts than from reading about them). For those of you who are already familiar with psychopharmacology, this book should provide easy reading from beginning to end. Going back and forth between the text and the graphics should provide interaction. Following review of the complete text, it should be simple to review the entire book by going through the graphics once again.

Expansion of *Essential Psychopharmacology* books

This fourth edition of *Essential Psychopharmacology* is the flagship, but not the entire fleet, as the *Essential Psychopharmacology* series has expanded now to an entire suite of products for the interested reader. For those of you interested in specific prescribing information, there are now three prescriber's guides:

- for psychotropic drugs, *Stahl's Essential Psychopharmacology: the Prescriber's Guide*
- for neurology drugs, *Essential Neuropharmacology: the Prescriber's Guide*
- for pain drugs: *Essential Pain Pharmacology: the Prescriber's Guide*

For those interested in how the textbook and prescriber's guides get applied in clinical practice there is a book covering 40 cases from my own clinical practice:

- *Case Studies: Stahl's Essential Psychopharmacology*

For teachers and students wanting to assess objectively their state of expertise, to pursue maintenance of certification credits for board recertification in psychiatry in the US, and for background on instructional design and how to teach there are two books:

- *Stahl's Self-Assessment Examination in Psychiatry: Multiple Choice Questions for Clinicians*
- *Best Practices in Medical Teaching*

For those interested in expanded visual coverage of specialty topics in psychopharmacology, there is the *Stahl's Illustrated* series:

- *Antidepressants*
- *Antipsychotics: Treating Psychosis, Mania and Depression*, 2nd edition
- *Anxiety, Stress, and PTSD*
- *Attention Deficit Hyperactivity Disorder*
- *Chronic Pain and Fibromyalgia*
- *Mood Stabilizers*
- *Substance Use and Impulsive Disorders*

Finally, there is an ever-growing edited series of subspecialty topics:

- *Next Generation Antidepressants*
- *Essential Evidence-Based Psychopharmacology*, 2nd edition
- *Essential CNS Drug Development*

Essential Psychopharmacology Online

Now, you also have the option of accessing all these books plus additional features online by going to *Essential Psychopharmacology Online* at **www.stahlonline.org**. We are proud to announce the continuing update of this new website which allows you to search online within the entire *Essential Psychopharmacology* suite of products. With publication of the fourth edition, two new features will become available on the website:

- downloadable slides of all the figures in the book
- narrated animations of several figures in the textbook, hyperlinked to the online version of the book, playable with a click

In addition, **www.stahlonline.org** is now linked to:

- our new journal *CNS Spectrums* (**www.journals.cambridge.org/CNS**), of which I am the new editor-in-chief, and which is now the official journal of the Neuroscience Education Institute (NEI), free online to NEI members. This journal now features readable and illustrated reviews of current topics in psychiatry, mental health, neurology, and the neurosciences as well as psychopharmacology
- the NEI website, **www.neiglobal.com**:
  - for CME credits for reading the books and the journal, and for completing numerous additional programs both online and live
  - for access to the live course and playback encore features from the annual NEI Psychopharmacology Congress
  - for access to the NEI Master Psychopharmacology Program, an online fellowship with certification
- plans for expansion to a Cambridge University Health Partners co-accredited online Masterclass and Certificate in Psychopharmacology, based upon live programs held on campus in Cambridge and taught by University of Cambridge faculty, including myself, having joined the faculty there as an Honorary Visiting Senior Fellow

Hopefully the reader can appreciate that this is an incredibly exciting time for the fields of neuroscience and mental health, creating fascinating opportunities for clinicians to utilize current therapeutics and to anticipate future medications that are likely to transform the field of psychopharmacology. Best wishes for your first step on this fascinating journey.

Stephen M. Stahl, MD, PhD

CME information

Release/expiration dates

Release date: February 1, 2013

CME credit expiration date: January 31, 2016 (*if this date has passed, please contact NEI for updated information)*

Target audience

This activity has been developed for prescribers specializing in psychiatry. There are no prerequisites. All other healthcare providers who are interested in psychopharmacology are welcome for advanced study, especially primary care physicians, nurse practitioners, psychologists, and pharmacists.

Statement of need

Psychiatric illnesses have a neurobiological basis and are primarily treated by pharmacological agents; understanding each of these, as well as the relationship between them, is essential in order to select appropriate treatment for a patient. The field of psychopharmacology has experienced incredible growth; it has also experienced a major paradigm shift from a limited focus on neurotransmitters and receptors to an emphasis as well upon brain circuits, neuroimaging, genetics, and signal transduction cascades.

The following unmet needs and professional practice gaps regarding mental health were revealed following a critical analysis of activity feedback, expert faculty assessment, literature review, and through new medical knowledge:

- Mental disorders are highly prevalent and carry substantial burden that can be alleviated through treatment; unfortunately, many patients with mental disorders do not receive treatment or receive suboptimal treatment.
- There is a documented gap between evidence-based practice guidelines and actual care in clinical practice for patients with mental illnesses.
- This gap is due at least in part to lack of clinician confidence and knowledge in terms of appropriate usage of the therapeutic tools available to them.

To help address clinician performance gaps with respect to diagnosis and treatment of mental health disorders, quality improvement efforts need to provide education regarding (1) the fundamentals of neurobiology as it relates to the most recent research regarding the neurobiology of mental illnesses; (2) the mechanisms of action of treatment options for mental illnesses and the relationship to the pathophysiology of the disease states; and (3) new therapeutic tools and research that are likely to affect clinical practice.

Learning objectives

After completing this activity, participants should be better able to

- apply fundamental principles of neurobiology to the assessment of psychiatric disease states
- differentiate the neurobiological targets for psychotropic medications
- link the relationship of psychotropic drug mechanism of action to the pathophysiology of disease states
- identify novel research and treatment approaches that are expected to affect clinical practice

Accreditation and credit designation statements

The Neuroscience Education Institute (NEI) is accredited by the Accreditation Council for Continuing Medical Education (ACCME) to provide continuing medical education for physicians.

The Neuroscience Education Institute designates this enduring material for a maximum of 67 *AMA PRA Category 1 Credits*™. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

Nurses: for all of your CE requirements for recertification, the ANCC will accept *AMA PRA Category 1 Credits*™ from organizations accredited by the ACCME.

Physician assistants: the NCCPA accepts *AMA PRA Category 1 Credits*™ from organizations accredited by the AMA (providers accredited by the ACCME).

A certificate of participation for completing this activity will also be available.

Activity instructions

This CME activity is in the form of a printed monograph and incorporates instructional design to enhance your retention of the information and pharmacological concepts that are being presented. You are advised to go through the figures in this activity from beginning to end, followed by the text, and then complete the posttests and evaluations. The estimated time for completion of this activity is 67 hours.

Instructions for CME credit

Certificates of CME credit or participation are available for each topical section of the book (total of 12 sections). To receive a section-specific certificate of CME credit or participation, please complete the relevant posttest and evaluation, available only online at www.neiglobal.com/CME (under "Book"). If a passing score of 70% or more is attained (required to receive credit), you can immediately print your certificate. There is a fee for each post test (varies per section), which is waived for NEI members. If you have questions, please call 888–535–5600, or email customerservice@neiglobal.com.

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These materials have been peer-reviewed to ensure the scientific accuracy and medical relevance of information presented and its independence from commercial bias. The Neuroscience Education Institute takes responsibility for the content, quality, and scientific integrity of this CME activity.

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Chapter 1

Chemical neurotransmission

Modern psychopharmacology is largely the story of chemical neurotransmission. To understand the actions of drugs on the brain, to grasp the impact of diseases upon the central nervous system, and to interpret the behavioral consequences of psychiatric medicines, one must be fluent in the language and principles of chemical neurotransmission. The importance of this fact cannot be overstated for the student of psychopharmacology. This chapter forms the foundation for the entire book, and the roadmap for one's journey through one of the most exciting topics in science today, namely the neuroscience of how disorders and drugs act upon the central nervous system.

Anatomical versus chemical basis of neurotransmission

What is neurotransmission? Neurotransmission can be described in many ways: anatomically, chemically, electrically. The *anatomical* basis of neurotransmission is neurons (Figures 1-1 through 1-3) and the connections between them, called synapses (Figure 1-4), sometimes also called the *anatomically addressed* nervous system, a complex of "hard-wired" synaptic connections between neurons, not unlike millions of telephone wires within thousands upon thousands of cables. The anatomically addressed brain is thus a complex wiring diagram, ferrying electrical impulses to wherever the "wire" is plugged in (i.e., at a synapse). Synapses can form on many parts of a neuron, not just the dendrites as axodendritic synapses, but also on the soma as axosomatic synapses, and even at the beginning and at the end of axons (axoaxonic synapses) (Figure 1-2). Such synapses are said to be "asymmetric" since communication is structurally designed to be in one direction; that is, anterograde from the axon of the first neuron to the dendrite, soma, or axon of the second neuron (Figures 1-2 and 1-3). This means that there are presynaptic elements that differ from postsynaptic elements (Figure 1-4). Specifically, neurotransmitter is packaged in the presynaptic nerve terminal like ammunition in a loaded gun, and then fired at the postsynaptic neuron to target its receptors.

Neurons are the cells of chemical communication in the brain. Human brains are comprised of tens of billions of neurons, and each is linked to thousands of other neurons. Thus, the brain has trillions of specialized connections known as synapses. Neurons

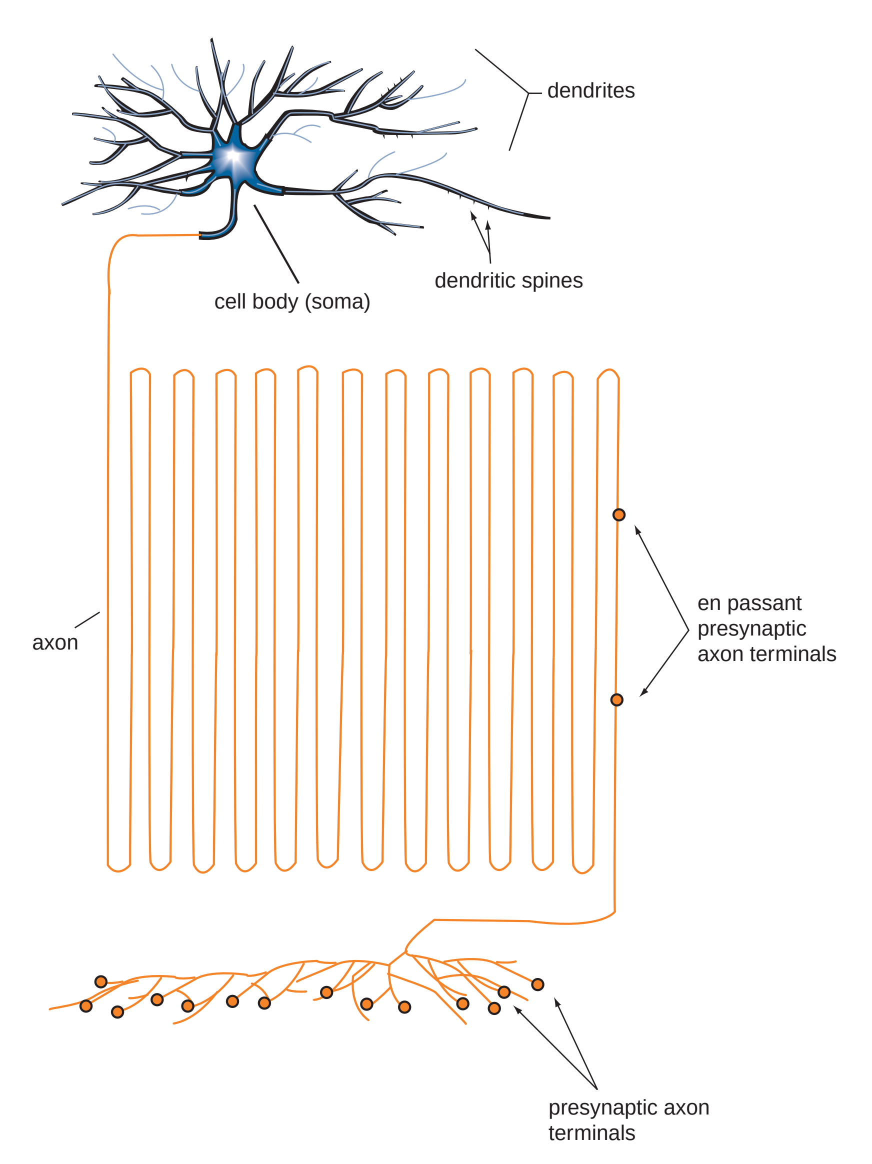


Figure 1-1. General structure of a neuron. This is an artist's conception of the generic structure of a neuron. All neurons have a cell body known as the soma, which is the command center of the nerve and contains the nucleus of the cell. All neurons are also set up structurally to both send and receive information. Neurons send information via an axon that forms presynaptic terminals as the axon passes by (en passant) or as the axon ends.

have many sizes, lengths, and shapes that determine their functions. Localization within the brain also determines function. When neurons malfunction, behavioral symptoms may occur. When drugs alter neuronal function, behavioral symptoms may be relieved, worsened, or produced.

General structure of a neuron. Although this textbook will often portray neurons with a generic structure (such as that shown in Figures 1-1 through 1-3), the truth is that many neurons have unique structures depending upon where in the brain they are located and what their function is. All neurons have a cell body known as the soma, and are set up structurally to receive information from other neurons through dendrites, sometimes via spines on the dendrites and often through an elaborately branching "tree" of dendrites (Figure 1-2). Neurons are also set up structurally to send information to other neurons via an axon that forms presynaptic terminals as the axon passes by (en passant, Figure 1-1) or as the axon ends (presynaptic axon terminals, Figures 1-1 through 1-4).

Neurotransmission has an *anatomical* infrastructure, but it is fundamentally a very elegant *chemical* operation. Complementary to the anatomically addressed nervous system is the *chemically addressed* nervous system, which forms the *chemical* basis of neurotransmission: namely, how chemical signals

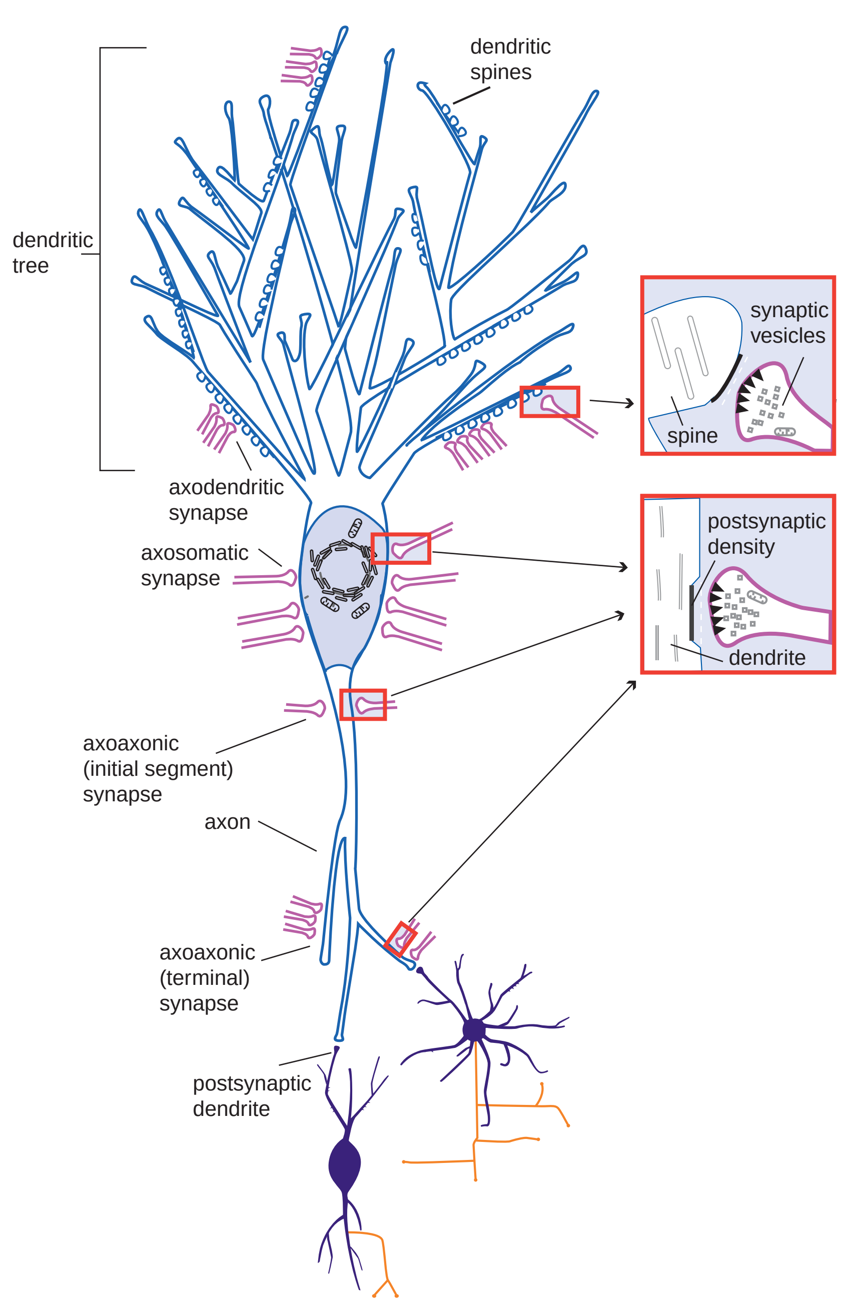


Figure 1-2. Axodendritic, axosomatic, and axoaxonic connections. After neurons migrate, they form synapses. As shown in this figure, synaptic connections can form not just between the axon and dendrites of two neurons (axodendritic) but also between the axon and the soma (axosomatic) or the axons of the two neurons (axoaxonic). Communication is anterograde from the axon of the first neuron to the dendrite, soma, or axon of the second neuron.

are coded, decoded, transduced, and sent along the way. Understanding the principles of chemical neurotransmission is a fundamental requirement for grasping how psychopharmacologic agents work, because they target key molecules involved in neurotransmission. Drug targeting of specific chemical sites that influence neurotransmission is discussed in Chapters 2 and 3.

Understanding the chemically addressed nervous system is also a prerequisite for becoming a "neurobiologically informed" clinician: that is, being able to translate exciting new findings on brain circuitry, functional neuroimaging, and genetics into clinical practice, and potentially improving the manner in which psychiatric disorders and their symptoms are diagnosed and treated. The chemistry of neurotransmission in specific

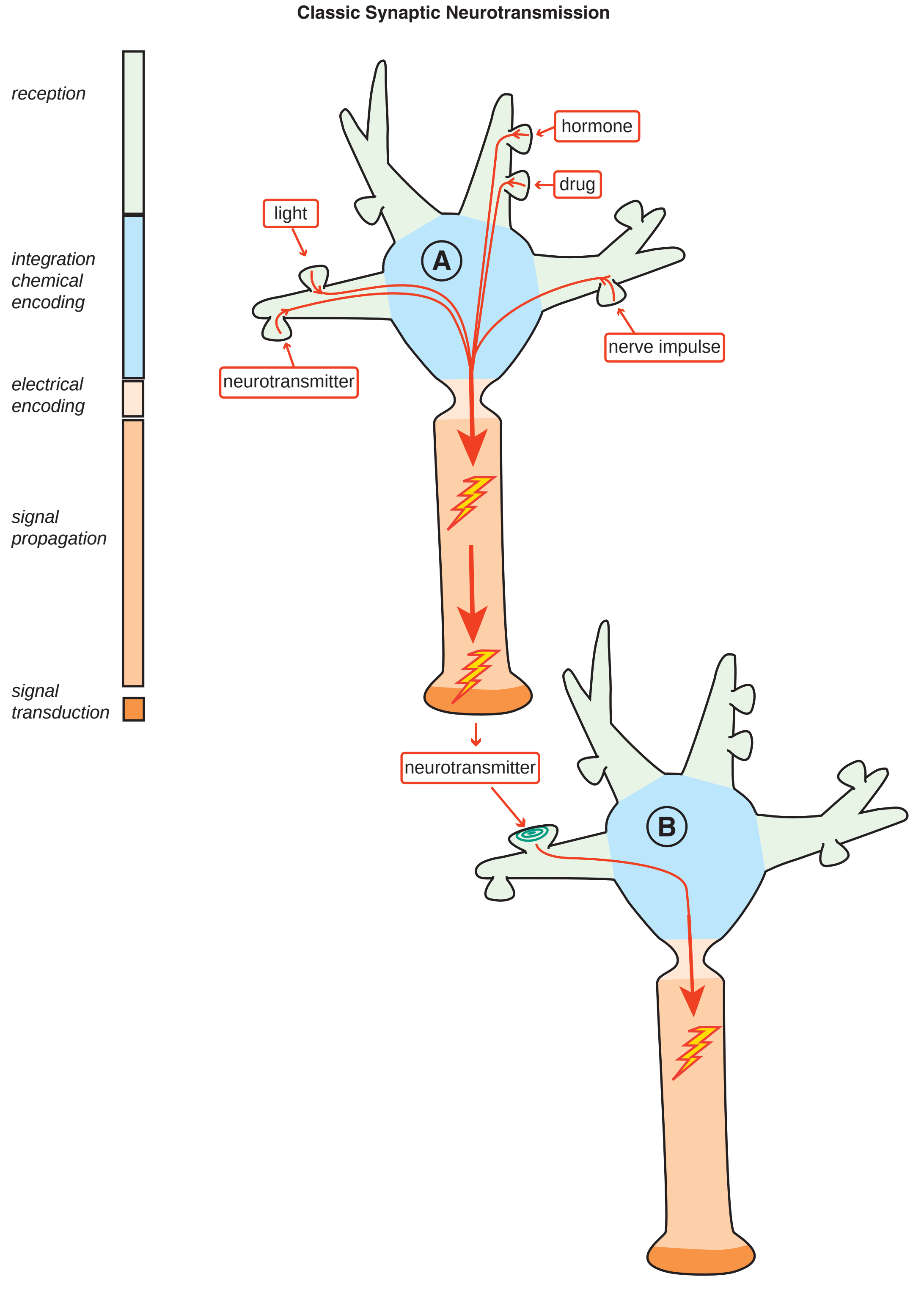


Figure 1-3. Classic synaptic neurotransmission. In classic synaptic neurotransmission, stimulation of a presynaptic neuron (e.g., by neurotransmitters, light, drugs, hormones, nerve impulses) causes electrical impulses to be sent to its axon terminal. These electrical impulses are then converted into chemical messengers and released to stimulate the receptors of a postsynaptic neuron. Thus, although communication *within* a neuron can be electrical, communication *between* neurons is chemical.

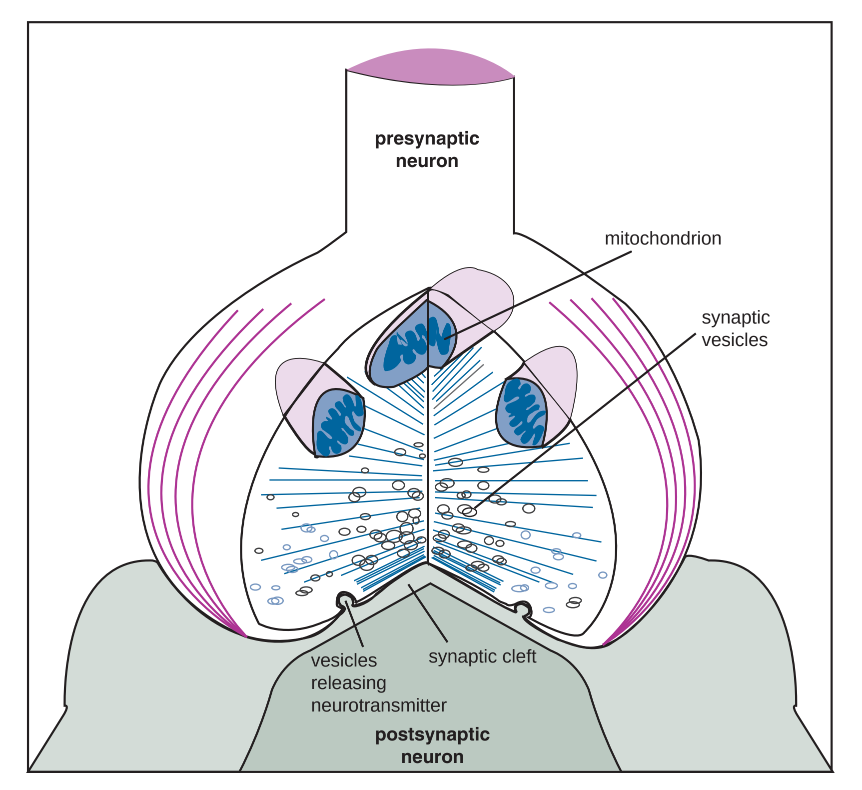


Figure 1-4. Enlarged synapse. The synapse is enlarged conceptually here to show the specialized structures that enable chemical neurotransmission to occur. Specifically, a presynaptic neuron sends its axon terminal to form a synapse with a postsynaptic neuron. Energy for neurotransmission from the presynaptic neuron is provided by mitochondria there. Chemical neurotransmitters are stored in small vesicles, ready for release upon firing of the presynaptic neuron. The synaptic cleft is the gap between the presynaptic neuron and the postsynaptic neuron; it contains proteins and scaffolding and molecular forms of "synaptic glue" to reinforce the connection between the neurons. Receptors are present on both sides of this cleft and are key elements of chemical neurotransmission.

brain regions and how these principles are applied to various specific psychiatric disorders and treated with various specific psychotropic drugs are discussed throughout the rest of the book.

Principles of chemical neurotransmission

Neurotransmitters

There are more than a dozen known or suspected neurotransmitters in the brain. For psychopharmacologists, it is particularly important to know the six key neurotransmitter systems targeted by psychotropic drugs:

- serotonin
- norepinephrine
- dopamine
- acetylcholine
- glutamate
- GABA (γ-aminobutyric acid)

Each is discussed in detail in the clinical chapters related to the specific drugs that target them. Other neurotransmitters that are also important neurotransmitters and neuromodulators, such as histamine and various neuropeptides and hormones, are mentioned in brief throughout the relevant clinical chapters in this textbook.

Some neurotransmitters are very similar to drugs and have been called "God's pharmacopeia." For example, it is well known that the brain makes its own morphine (i.e., β-endorphin) and its own marijuana (i.e., anandamide). The brain may even make its own antidepressants, anxiolytics, and hallucinogens. Drugs often mimic the brain's natural neurotransmitters, and some drugs have been discovered prior to the natural neurotransmitter. Thus, morphine was used in clinical practice before the discovery of β-endorphin; marijuana was smoked before the discovery of cannabinoid receptors and anandamide; the benzodiazepines Valium (diazepam) and Xanax (alprazolam) were

prescribed before the discovery of benzodiazepine receptors; and the antidepressants Elavil (amitriptyline) and Prozac (fluoxetine) entered clinical practice before molecular clarification of the serotonin transporter site. This underscores the point that the great majority of drugs that act in the central nervous system act upon the process of neurotransmission. Indeed, this apparently occurs at times in a manner that can mimic the actions of the brain itself, when the brain uses its own chemicals.

Input to any neuron can involve many different neurotransmitters coming from many different neuronal circuits. Understanding these inputs to neurons within functioning circuits can provide a rational basis for selecting and combining therapeutic agents. This theme is discussed extensively in each chapter on the various psychiatric disorders. The idea is that for the modern psychopharmacologist to influence abnormal neurotransmission in patients with psychiatric disorders, it may be necessary to target neurons in specific circuits. Since these networks of neurons send and receive information via a variety of neurotransmitters, it may therefore be not only rational but necessary to use multiple drugs with multiple neurotransmitter actions for patients with psychiatric disorders, especially if single agents with single neurotransmitter mechanisms are not effective in relieving symptoms.

Neurotransmission: classic, retrograde, and volume

Classic neurotransmission begins with an electrical process by which neurons send electrical impulses from one part of the cell to another part of the same cell via their axons (see neuron A in Figure 1-3). However, these electrical impulses do not jump directly to other neurons. Classic neurotransmission between neurons involves one neuron hurling a chemical messenger, or neurotransmitter, at the receptors of a second neuron (see the synapse between neuron A and neuron B in Figure 1-3). This happens frequently but not exclusively at the sites of synaptic connections. In the human brain, a hundred billion neurons each make thousands of synapses with other neurons for an estimated trillion chemically neurotransmitting synapses.

Communication *between* all these neurons at synapses is chemical, not electrical. That is, an electrical impulse in the first neuron is converted to a chemical signal at the synapse between it and a second neuron, in a process known as excitation–secretion coupling, the first stage of chemical neurotransmission. This occurs predominantly but not exclusively in one direction, from the *presynaptic* axon terminal to a second *postsynaptic* neuron (Figures 1-2 and 1-3). Finally, neurotransmission continues in the second neuron either by converting the chemical information from the first neuron back into an electrical impulse in the second neuron, or, perhaps more elegantly, by the chemical information from the first neuron triggering a cascade of further chemical messages within the second neuron to change that neuron's molecular and genetic functioning (Figure 1-3).

An interesting twist to chemical neurotransmission is the discovery that postsynaptic neurons can also "talk back" to their presynaptic neurons. They can do this via *retrograde neurotransmission* from the second neuron to the first at the synapse between them (Figure 1-5, right panel). Chemicals produced specifically as retrograde neurotransmitters at some synapses include the endocannabinoids (EC, also known as "endogenous marijuana"), which are synthesized in the postsynaptic neuron. They are then released and diffuse to presynaptic cannabinoid receptors such as the CB1 or cannabinoid 1 receptor (Figure 1-5, right panel). Another retrograde neurotransmitter is the gaseous neurotransmitter NO, or nitric oxide, which is synthesized postsynaptically and then diffuses out of the postsynaptic membrane and into the presynaptic membrane to interact with cyclic guanosine monophosphate (cGMP)-sensitive targets there (Figure 1-5, right panel). A third group of retrograde neurotransmitter are neurotrophic factors such as NGF (nerve growth factor), which is released from postsynaptic sites and then diffuses to the presynaptic neuron, where it is taken up into vesicles and transported all the way back to the cell nucleus via retrograde transport systems to interact with the genome there (Figure 1-5, right panel). What these retrograde neurotransmitters have to say to the presynaptic neuron and how this modifies or regulates the communication between pre- and postsynaptic neuron are subjects of intense active investigation.

In addition to "reverse" or retrograde neurotransmission at synapses, some neurotransmission does not need a synapse at all! Neurotransmission without a synapse is called *volume neurotransmission*, or nonsynaptic diffusion neurotransmission (examples are shown in Figures 1-6 through 1-8). Chemical messengers sent by one neuron to another can spill over to

Classic Neurotransmission Versus Retrograde Neurotransmission

A

A

Classic

NGF

NGF

cGMP-
sensitive
targets

CB1
receptor

NGF

NGF

EC

EC

NO
(nitric oxide)

NGF
(nerve growth
factor)

Retrograde

Figure 1-5. Retrograde neurotransmission. Not all neurotransmission is classic or anterograde or from top to bottom – namely, presynaptic to postsynaptic (left). Postsynaptic neurons may also communicate with presynaptic neurons from the bottom to the top via retrograde neurotransmission, from postsynaptic neuron to presynaptic neuron (right). Some neurotransmitters produced specifically as retrograde neurotransmitters at some synapses include the endocannabinoids (ECs, or "endogenous marijuana"), which are synthesized in the postsynaptic neuron, released, and diffuse to presynaptic cannabinoid receptors such as the cannabinoid 1 receptor (CB1); the gaseous neurotransmitter nitric oxide (NO), which is synthesized postsynaptically and then diffuses both out of the postsynaptic membrane and into the presynaptic membrane to interact with cyclic guanosine monophosphate (cGMP)-sensitive targets there; and neurotrophic factors such as nerve growth factor (NGF), which is released from postsynaptic sites and diffuses to the presynaptic neuron, where it is taken up into vesicles and transported all the way back to the cell nucleus via retrograde transport systems to interact with the genome there.

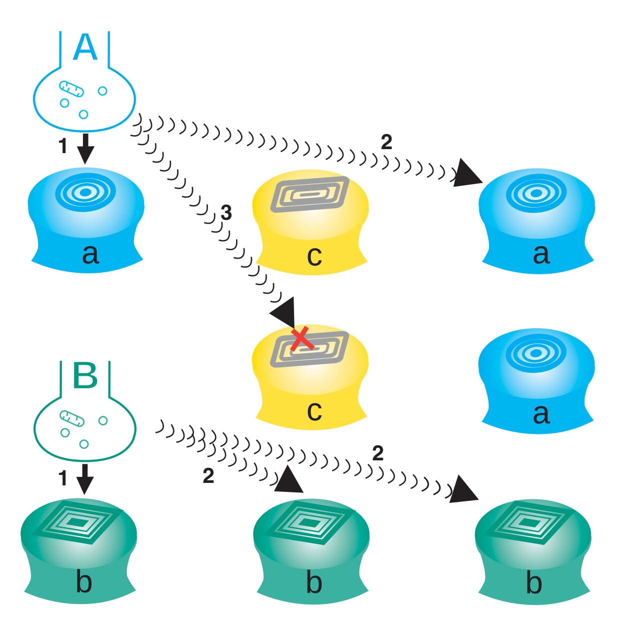


Figure 1-6. Volume neurotransmission. Neurotransmission can also occur without a synapse; this is called volume neurotransmission or nonsynaptic diffusion. In this figure, two anatomically addressed synapses (neurons A and B) are shown communicating with their corresponding postsynaptic receptors (a and b, arrows 1). However, there are also receptors for neurotransmitter A, neurotransmitter B, and neurotransmitter C, which are distant from the synaptic connections of the anatomically addressed nervous system. If neurotransmitter A or B can diffuse away from its synapse before it is destroyed, it will be able to interact with other matching receptor sites distant from its own synapse (arrows 2). If neurotransmitter A or B encounters a different receptor not capable of recognizing it (receptor c), it will not interact with that receptor even if it diffuses there (arrow 3). Thus, a chemical messenger sent by one neuron to another can spill over by diffusion to sites distant from its own synapse. Neurotransmission can occur at a compatible receptor within the diffusion radius of the matched neurotransmitter. This is analogous to modern communication with cellular telephones, which function within the transmitting radius of a given cell. This concept is called the chemically addressed nervous system, in which neurotransmission occurs in chemical "puffs." The brain is thus not only a collection of wires but also a sophisticated "chemical soup."

sites distant to the synapse by diffusion (Figure 1-6). Thus, neurotransmission can occur at any compatible receptor within the diffusion radius of the neurotransmitter, not unlike modern communication with cellular telephones, which function within the transmitting radius of a given cell tower (Figure 1-6). This concept is part of the chemically addressed nervous system, and here neurotransmission occurs in chemical "puffs" (Figures 1-6 through 1-8). The brain is thus not only a collection of wires, but also a sophisticated "chemical soup." The chemically addressed

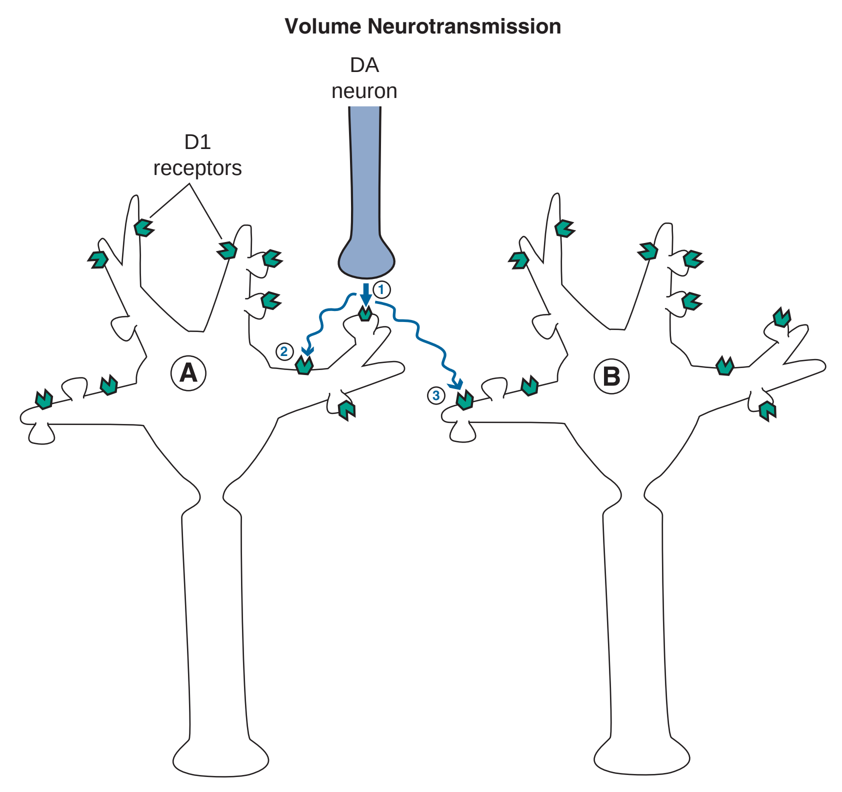


Figure 1-7. Volume neurotransmission: dopamine. An example of volume neurotransmission would be that of dopamine in the prefrontal cortex. Since there are few dopamine reuptake pumps in the prefrontal cortex, dopamine is available to diffuse to nearby receptor sites. Thus, dopamine released from a synapse (arrow 1) targeting postsynaptic neuron A is free to diffuse further in the absence of a reuptake pump and can reach dopamine receptors on that same neuron but outside of the synapse from which it was released, on neighboring dendrites (arrow 2). Shown here is dopamine also reaching extrasynaptic receptors on a neighboring neuron (arrow 3).

nervous system is particularly important in mediating the actions of drugs that act at various neurotransmitter receptors, since such drugs will act wherever there are relevant receptors, and not just where such receptors are innervated with synapses by the anatomically addressed nervous system. Modifying volume neurotransmission may indeed be a major way in which several psychotropic drugs work in the brain.

A good example of volume neurotransmission is dopamine action in the prefrontal cortex. Here there are very few dopamine reuptake transport pumps (dopamine transporters or DATs) to terminate the action of dopamine released in the prefrontal cortex during neurotransmission. This is much different from other brain areas, such as the striatum, where dopamine reuptake pumps are present in abundance. Thus, when dopamine neurotransmission occurs at a synapse in the prefrontal cortex, dopamine is free to spill over from that synapse and diffuse to neighboring dopamine receptors to stimulate them, even though there is no synapse at these "spillover" sites (Figure 1-7).

Another important example of volume neurotransmission is at the sites of autoreceptors on monoamine neurons (Figure 1-8). At the somatodendritic end of the neuron (top of the neurons in Figure 1-8) are autoreceptors that inhibit the release of neurotransmitter from the axonal end of the neuron (bottom of the neurons in Figure 1-8). Although some recurrent axon collaterals and other monoamine neurons may directly innervate somatodendritic receptors, these so-called somatodendritic autoreceptors also receive neurotransmitter from dendritic release (Figure 1-8, middle and right panels). There is no synapse here, just neurotransmitter leaked from the neuron upon its own receptors. The nature of a neuron's regulation by its somatodendritic autoreceptors is a subject of intense interest, and is theoretically linked to the mechanism of action of many antidepressants, as will be explained in Chapter 7. The take-home point here is that not all chemical neurotransmission occurs at synapses.

Excitation–secretion coupling

An electrical impulse in the first – or presynaptic – neuron is converted into a chemical signal at the synapse by a process known as *excitation–secretion*

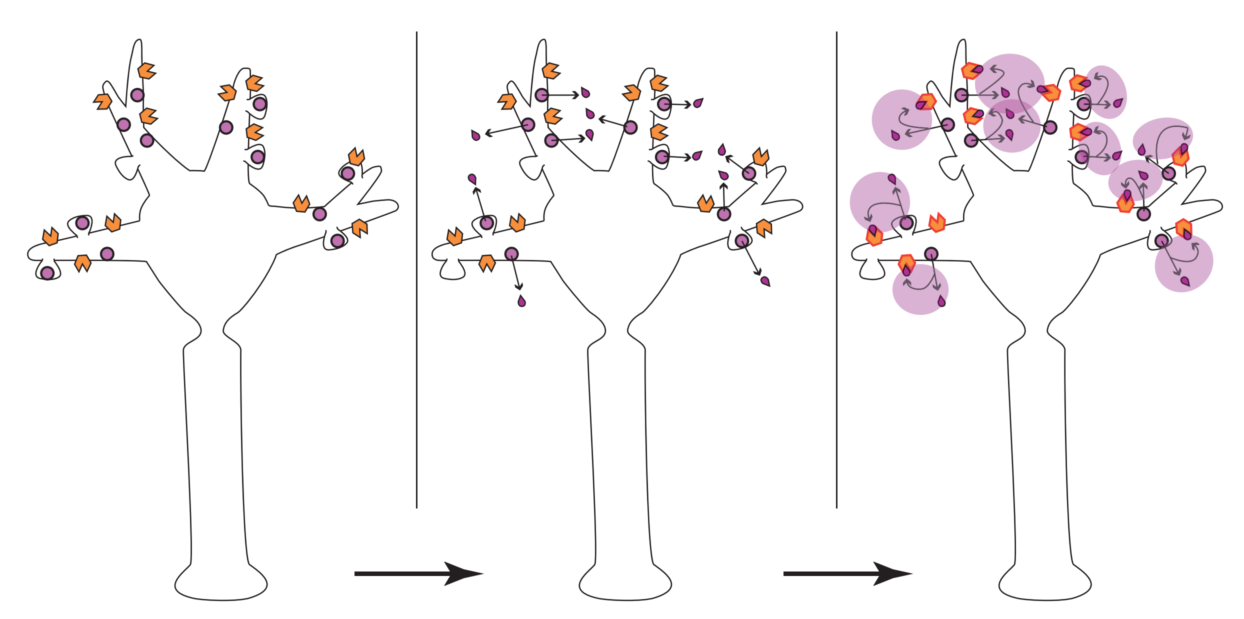


Figure 1-8. Volume neurotransmission: monoamine autoreceptors. Another example of volume neurotransmission could involve autoreceptors on monoamine neurons. Autoreceptors located on the dendrites and soma of a neuron (at the top of the neuron in the left panel) normally inhibit release of neurotransmitter from the axon of that neuron (at the bottom of the neuron in the left panel), and thus inhibit impulse flow through that neuron from top to bottom. Monoamines released from the dendrites of this neuron (at the top of the neuron in the middle panel), then bind to these autoreceptors (at the top of the neuron in the right panel) and would inhibit neuronal impulse flow in that neuron (from the bottom of the neuron in the right panel). This action occurs due to volume neurotransmission and despite the absence of synaptic neurotransmission in the somatodendritic areas of these neurons.

coupling. Once an electrical impulse invades the presynaptic axon terminal, it causes the release of chemical neurotransmitter stored there (Figures 1-3 and 1-4). Electrical impulses open ion channels – both *voltage-sensitive sodium channels* (VSSCs) and *voltage-sensitive calcium channels* (VSCCs) – by changing the ionic charge across neuronal membranes. As sodium flows into the presynaptic nerve through sodium channels in the axon membrane, the electrical charge of the action potential moves along the axon until it reaches the presynaptic nerve terminal, where it also opens calcium channels. As calcium flows into the presynaptic nerve terminal, it causes synaptic vesicles anchored to the inner membrane to spill their chemical contents into the synapse. The way is paved for chemical communication by previous synthesis of neurotransmitter and storage of neurotransmitter in the first neuron's presynaptic axon terminal.

Excitation–secretion coupling is thus the way that the neuron transduces an electrical stimulus into a chemical event. This happens very quickly once the electrical impulse enters the presynaptic neuron. It is also possible for the neuron to transduce a chemical message from a presynaptic neuron back into an electrical chemical message in the postsynaptic neuron by opening ion channels linked to neurotransmitters there. This also happens very quickly when chemical neurotransmitters open ion channels that change the flow of charge into the neuron, and ultimately, action potentials in the postsynaptic neuron. Thus, the process of neurotransmission is constantly transducing chemical signals into electrical signals, and electrical signals back into chemical signals.

Signal transduction cascades

Overview

Neurotransmission can be seen as part of a much larger process than just the communication of a presynaptic axon with a postsynaptic neuron at the

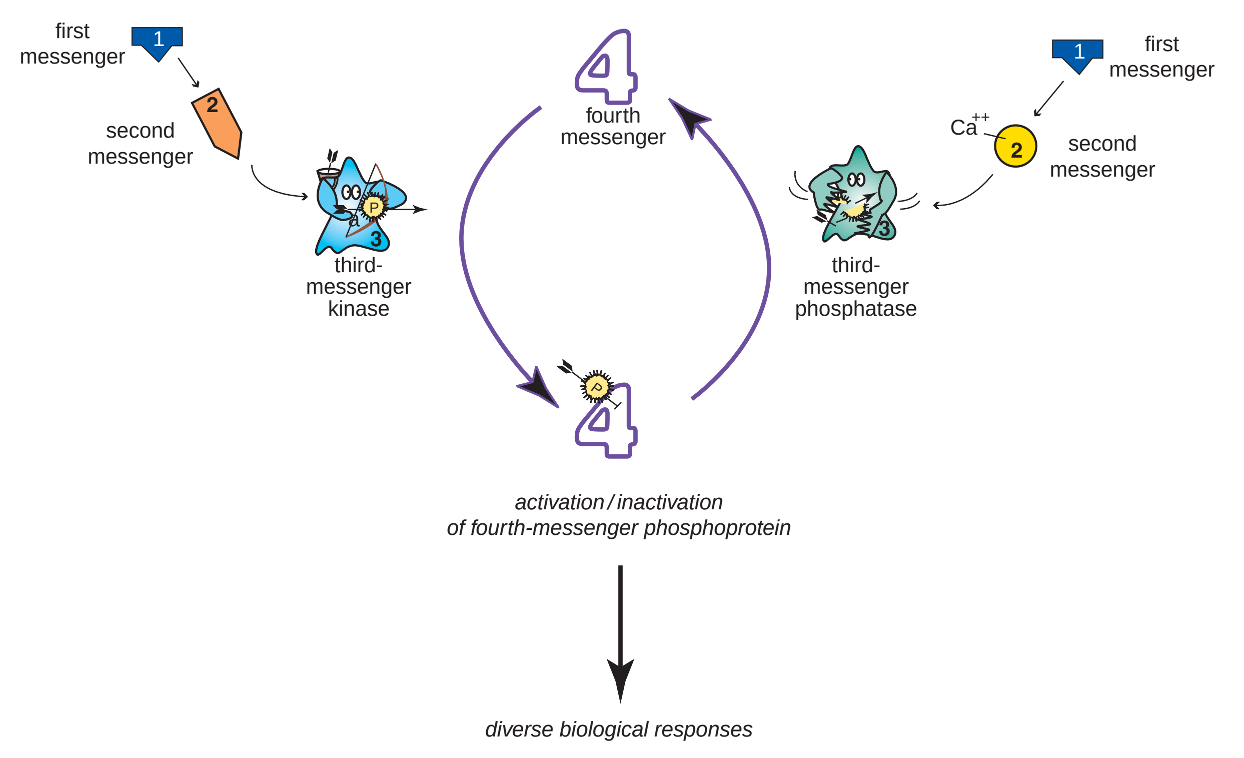


Figure 1-9. Signal transduction cascade. The cascade of events that occurs following stimulation of a postsynaptic receptor is known as signal transduction. Signal transduction cascades can activate third-messenger enzymes known as kinases, which add phosphate groups to proteins to create phosphoproteins (on the left). Other signal transduction cascades can activate third-messenger enzymes known as phosphatases, which remove phosphates from phosphoproteins (on the right). The balance between kinase and phosphatase activity, signaled by the balance between the two neurotransmitters that activate each of them, determines the degree of downstream chemical activity that gets translated into diverse biological responses, such as gene expression and synaptogenesis.

synapse between them. That is, neurotransmission can also be seen as communication from the genome of the presynaptic neuron (neuron A in Figure 1-3) to the genome of the postsynaptic neuron (neuron B in Figure 1-3), and then back from the genome of the postsynaptic neuron to the genome of the presynaptic neuron via retrograde neurotransmission (right panel in Figure 1-5). Such a process involves long strings of chemical messages within both presynaptic and postsynaptic neurons, called signal transduction cascades.

Signal transduction cascades triggered by chemical neurotransmission thus involve numerous molecules, starting with neurotransmitter first messenger, and proceeding to second, third, fourth, and more messengers (Figures 1-9 through 1-30). The initial events occur in less than a second, but the long-term consequences are mediated by downstream messengers that take hours to days to activate, yet can last for many days or even for the lifetime of a synapse or neuron (Figure 1-10). Signal transduction cascades are somewhat akin to a molecular "pony express" with specialized molecules acting as a sequence of riders, handing on the message to the next specialized molecule, until the message has reached a functional destination, such as gene expression or activation of otherwise "sleeping" and inactive molecules (see for example, Figures 1-9 through 1-19).

An overview of such a molecular "pony express," from first-messenger neurotransmitter through several "molecular riders" to the production of diverse biological responses, is shown in Figure 1-9. Specifically, a first-messenger neurotransmitter on the left activates the production of a chemical second messenger that in turn activates a third messenger, namely an enzyme known as a kinase that adds phosphate groups to fourth-messenger proteins to create phosphoproteins (Figure 1-9, left). Another signal transduction cascade is shown on the right with a first-messenger neurotransmitter opening an ion channel that allows calcium to enter the neuron and

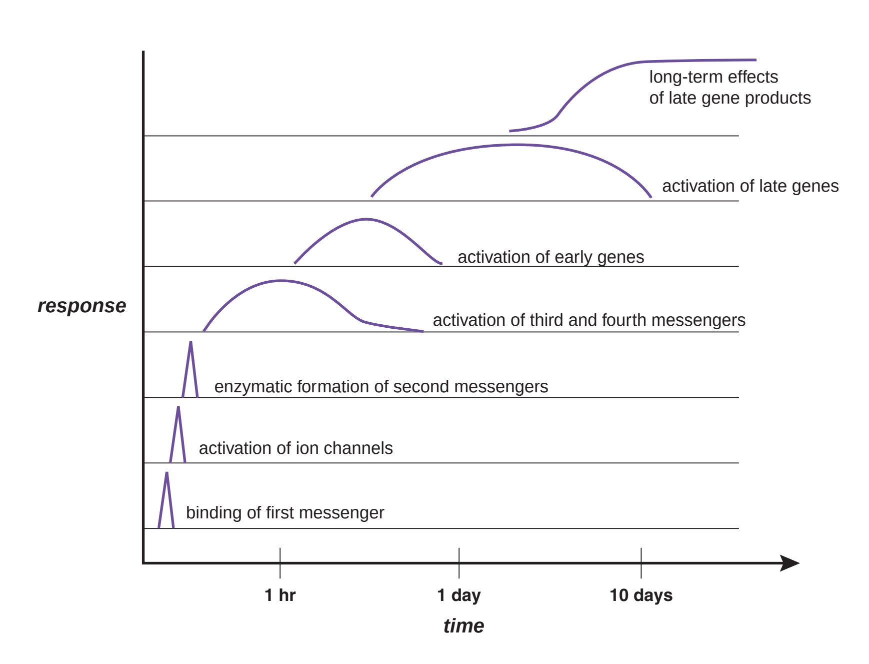


Figure 1-10. Time course of signal transduction. The time course of signal transduction is shown here. The process begins with binding of a first messenger (bottom), which leads to activation of ion channels or enzymatic formation of second messengers. This, in turn, can cause activation of third and fourth messengers, which are often phosphoproteins. If genes are subsequently activated, this leads to the synthesis of new proteins, which can alter the neuron's functions. Once initiated, the functional changes due to protein activation or new protein synthesis can last for at least many days and possibly much longer. Thus, the ultimate effects of signal transduction cascades triggered by chemical neurotransmission are not only delayed but also long-lasting.

act as the second messenger for this cascade system (Figure 1-9, right). Calcium then activates a different third messenger, namely an enzyme known as a phosphatase that removes phosphate groups from fourth-messenger phosphoproteins and thus reverses the actions of the third messenger on the left. The balance between kinase and phosphatase activity, signaled by the balance between the two neurotransmitters that activate each of them, determines the degree of downstream chemical activity that gets translated into active fourth messengers able to trigger diverse biological responses, such as gene expression and synaptogenesis (Figure 1-9). Each molecular site within the transduction cascade of chemical and electrical messages is a potential location for a malfunction associated with a mental illness; it is also a potential target for a psychotropic drug. Thus, the various elements of multiple signal transduction cascades play very important roles in psychopharmacology.

Four of the most important signal transduction cascades in the brain are shown in Figure 1-11. These include G-protein-linked systems, ion-channel-linked systems, hormone-linked systems, and neurotrophin-linked systems. There are many chemical messengers for each of these four critical signal transduction cascades; the G-protein-linked and the ion-channel-linked cascades are triggered by neurotransmitters (Figure 1-11). Many of the psychotropic drugs used in clinical practice today target one of these two signal transduction cascades. Drugs that target the G-protein-linked system are discussed in Chapter 2; drugs that target the ion-channel-linked system are discussed in Chapter 3.

Forming a second messenger

Each of the four signal transduction cascades (Figure 1-11) passes its message from an extracellular first messenger to an intracellular second messenger. In the case of G-protein-linked systems, the second messenger is a chemical, but in the case of an ion-channel-linked system, the second messenger can be an ion such as calcium (Figure 1-11). For some hormone-linked systems, a second messenger is formed when the hormone finds its receptor in the cytoplasm and binds to it to form a hormone–nuclear receptor complex (Figure 1-11). For neurotrophins, a complex set of various second messengers exist (Figure 1-11), including proteins that are kinase enzymes with an alphabet soup of complicated names.

The transduction of an extracellular first neurotransmitter from the presynaptic neuron into an intracellular second messenger in the postsynaptic neuron is known in detail for some second-messenger

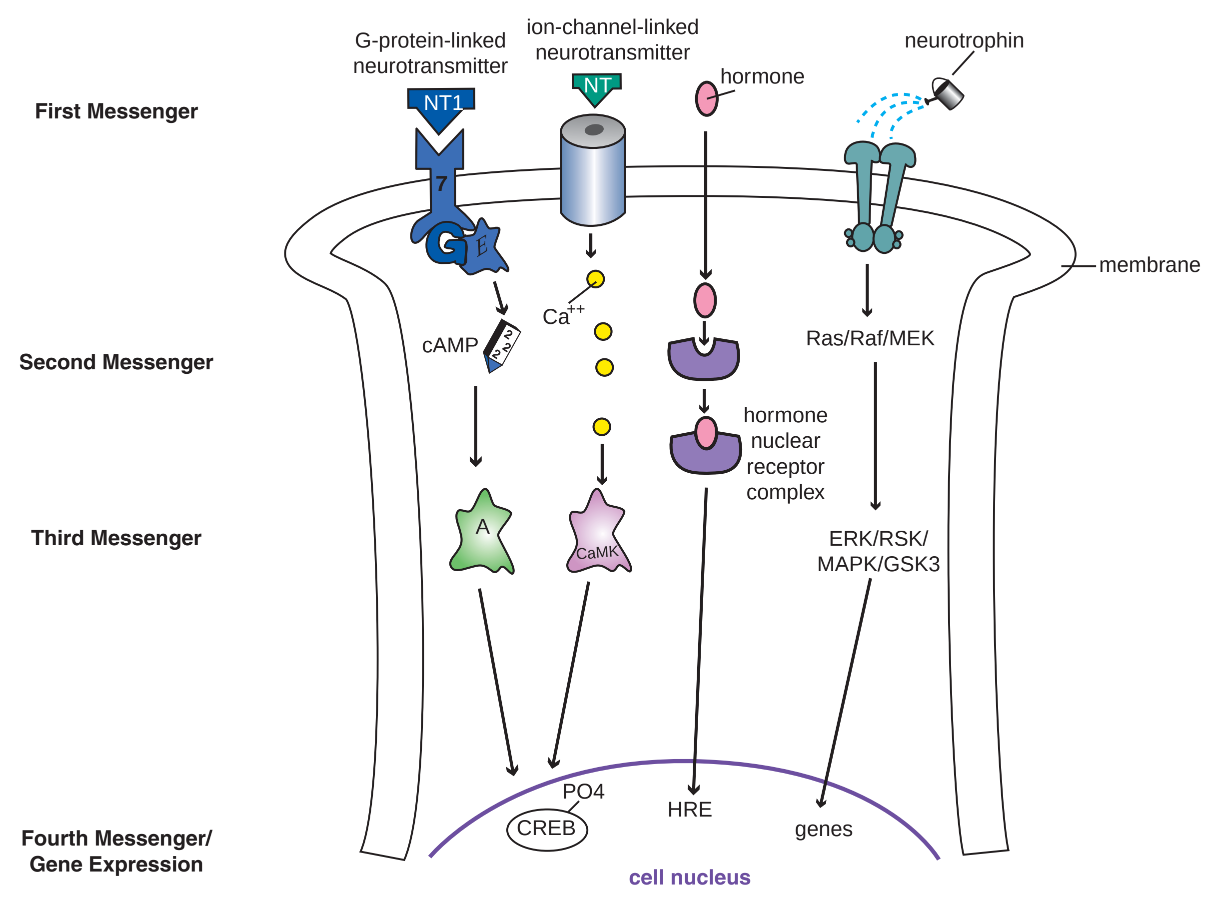


Figure 1-11. Different signal transduction cascades. Four of the most important signal transduction cascades in the brain are shown here. These include G-protein-linked systems, ion-channel-linked systems, hormone-linked systems, and neurotrophin-linked systems. Each begins with a different first messenger binding to a unique receptor, leading to activation of very different downstream second, third, and subsequent chemical messengers. Having many different signal transduction cascades allows neurons to respond in amazingly diverse biological ways to a whole array of chemical messaging systems. Neurotransmitters (NT) activate both the G-protein-linked system and the ion-channel-linked system on the left, and both of these systems activate genes in the cell nucleus by phosphorylating a protein there called cAMP response element-binding protein (CREB). The G-protein-linked system works through a cascade involving cAMP (cyclic adenosine monophosphate) and protein kinase A, whereas the ion-channel-linked system works through calcium and its ability to activate a different kinase called calcium/calmodulin-dependent protein kinase (CaMK). Certain hormones, such as estrogen and other steroids, can enter the neuron, find their receptors in the cytoplasm, and bind them to form a hormone–nuclear receptor complex. This complex can then enter the cell nucleus to interact with hormone response elements (HRE) there to trigger activation of specific genes. Finally, the neurotrophin system on the far right activates a series of kinase enzymes, with a confusing alphabet soup of names, to trigger gene expression, which may control such functions as synaptogenesis and neuronal survival. Ras is a G protein, Raf is a kinase, and the other elements in this cascade are proteins as well (MEK stands for mitogen-activated protein kinase/extracellular-signal-regulated kinase; ERK stands for extracellular-signal-regulated kinase itself; RSK is ribosomal S6 kinase; MAPK is MAP kinase itself, and GSK-3 is glycogen synthase kinase 3).

systems, such as those that are linked to G proteins (Figures 1-12 through 1-15). There are four key elements to this second-messenger system:

- the first-messenger neurotransmitter;
- a receptor for the neurotransmitter that belongs to the receptor superfamily in which all have the structure of seven transmembrane regions (designated by the number 7 on the receptor in Figures 1-12 through 1-15);
- a G protein capable of binding both to certain conformations of the neurotransmitter receptor (7) and to an enzyme system (E) that can synthesize the second messenger;
- and finally the enzyme system itself for the second messenger.

The first step is the neurotransmitter binding to its receptor (Figure 1-13). This changes the conformation of the receptor so it can now fit with the G protein, as

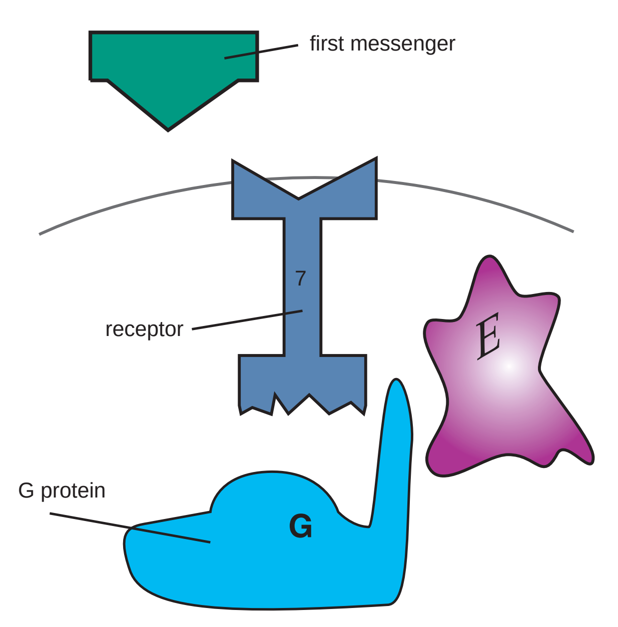


Figure 1-12. Elements of G-protein-linked system. Shown here are the four elements of a G-protein-linked second-messenger system. The first element is the neurotransmitter itself, sometimes also referred to as the first messenger. The second element is the G-protein-linked neurotransmitter receptor, which is a protein with seven transmembrane regions. The third element, a G protein, is a connecting protein. The fourth element of the second-messenger system is an enzyme (E), which can synthesize a second messenger when activated.

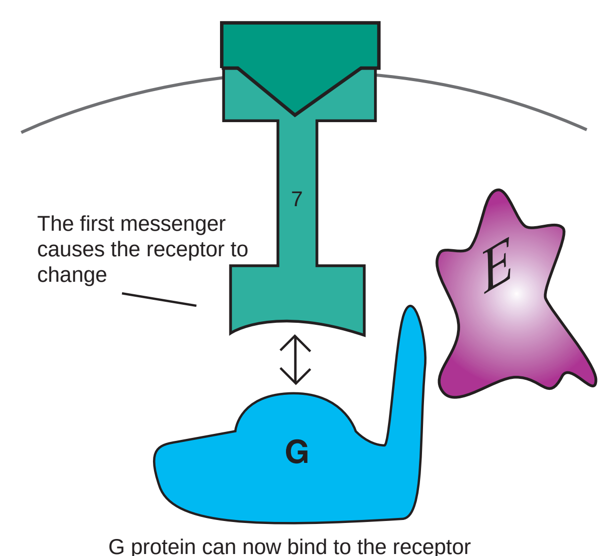


Figure 1-13. First messenger. In this figure, the neurotransmitter has docked into its receptor. The first messenger does its job by transforming the conformation of the receptor so that the receptor can bind to the G protein, indicated here by the receptor turning the same color as the neurotransmitter and changing its shape at the bottom in order to make it capable of binding to the G protein.

indicated by the receptor (7) turning green and its shape changing at the bottom. Next comes the binding of the G protein to this new conformation of the receptor–neurotransmitter complex (Figure 1-14). The two receptors cooperate with each other: namely, the neurotransmitter receptor itself and the G protein, which can be thought of as another type of receptor associated with the inner membrane of the cell. This cooperation is indicated in Figure 1-14 by the G protein turning green and its conformation changing on the right so it is now capable of binding to an enzyme (E) that synthesizes the second messenger. Finally, the enzyme, in this case adenylate cyclase, binds to the G protein and synthesizes cAMP (cyclic adenosine monophosphate), which serves as second messenger (Figure 1-15). This is indicated in Figure 1-15 by the enzyme turning green and generating cAMP (the icon with number 2 on it).

Beyond the second messenger to phosphoprotein messengers

Recent research has begun to clarify the complex molecular links between the second messenger and its ultimate effects upon cellular functions. These links are specifically the third, fourth, and subsequent chemical messengers in the signal transduction cascades shown in Figures 1-9, 1-11, and 1-16 through 1-30. Each of the four classes of signal transduction cascades shown in Figure 1-11 not only begins with a different first messenger binding to a unique receptor, but also leads to activation of very different downstream second, third, and subsequent chemical messengers. Having many different signal transduction cascades allows neurons to respond in amazingly diverse biological ways to a whole array of chemical messaging systems.

What is the ultimate target of signal transduction? There are two major targets of signal transduction: phosphoproteins and genes. Many of the intermediate targets along the way to the gene are phosphoproteins, such as the fourth-messenger phosphoproteins shown in Figures 1-18 and 1-19 that lie dormant in the neuron until signal transduction wakes them up and they can spring into action.

The actions shown in Figure 1-9 on fourth-messenger phosphoproteins as targets of signal transduction can be seen in more detail in Figures 1-16 through 1-19. Thus, one signal transduction pathway can activate a third-messenger kinase through second-messenger cAMP (Figure 1-16), whereas another signal transduction pathway can activate a third-messenger phosphatase through second-messenger calcium

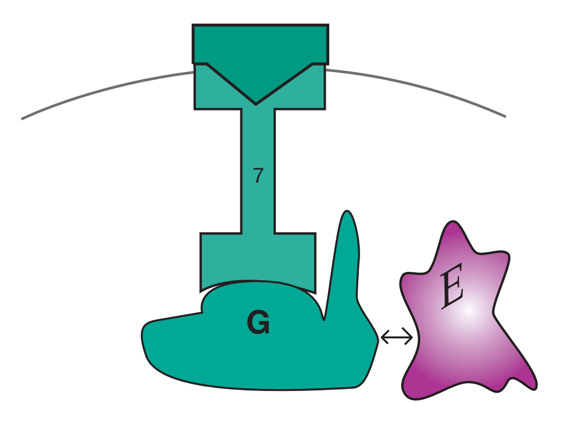


Figure 1-14. G protein. The next stage in producing a second messenger is for the transformed neurotransmitter receptor to bind to the G protein, depicted here by the G protein turning the same color as the neurotransmitter and its receptor. Binding of the binary neurotransmitter receptor complex to the G protein causes yet another conformational change, this time in the G protein, represented here as a change in the shape of the right-hand side of the G protein. This prepares the G protein to bind to the enzyme capable of synthesizing the second messenger.

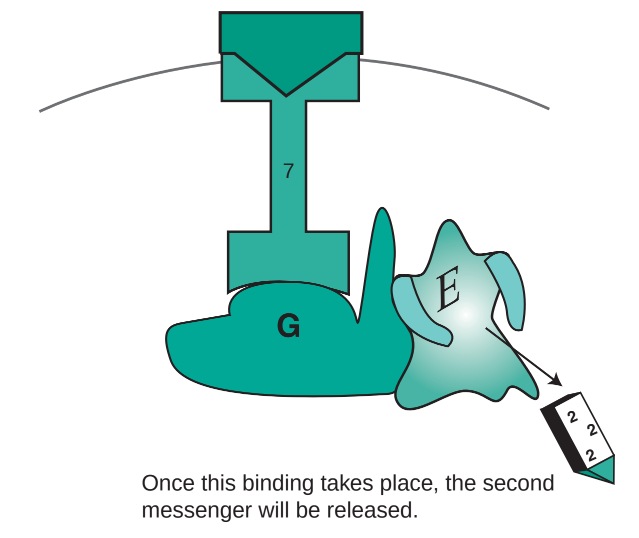


Figure 1-15. Second messenger. The final step in formation of the second messenger is for the ternary complex neurotransmitter–receptor–G protein to bind to a messenger-synthesizing enzyme, depicted here by the enzyme turning the same color as the ternary complex. Once the enzyme binds to this ternary complex, it becomes activated and capable of synthesizing the second messenger. Thus, it is the cooperation of all four elements, wrapped together as a quaternary complex, that leads to the production of the second messenger. Information from the first messenger thus passes to the second messenger through use of receptor–G protein–enzyme intermediaries.

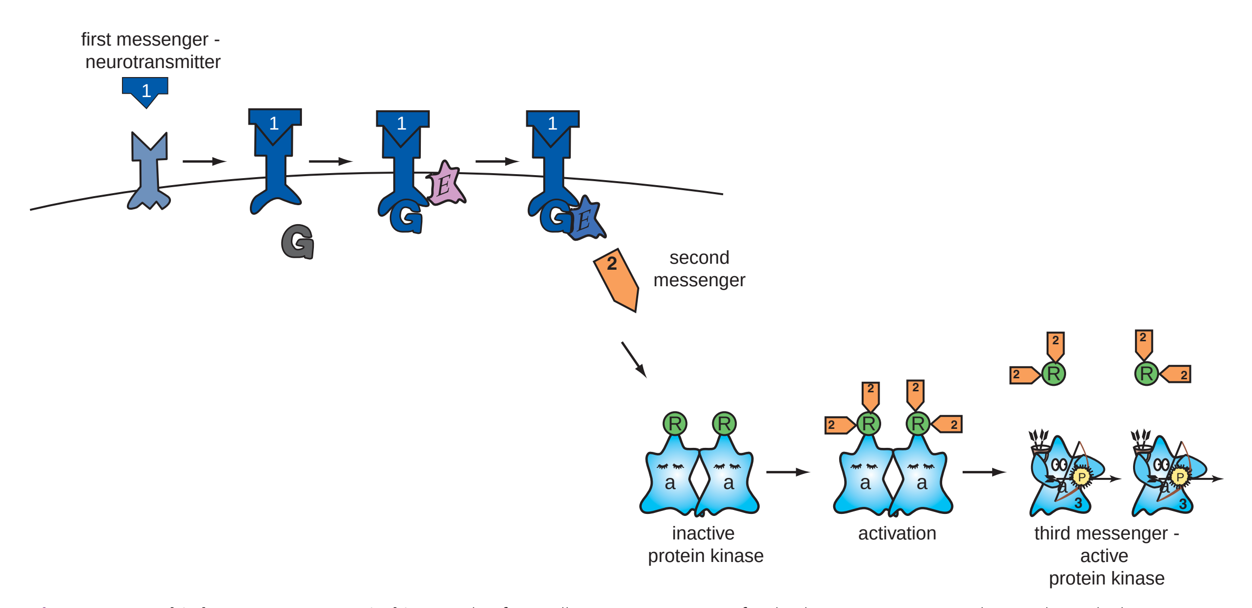


Figure 1-16. Third-messenger protein kinase. This figure illustrates activation of a third-messenger protein kinase through the second-messenger cAMP. Neurotransmitters begin the process of activating genes by producing a second messenger (cAMP), as shown in Figures 1-12 through 1-15. Some second messengers activate intracellular enzymes known as protein kinases. This enzyme is shown here as inactive when it is paired with another copy of the enzyme plus two regulatory units (R). In this case, two copies of the second messenger interact with the regulatory units, dissociating them from the protein kinase dimer. This dissociation activates each protein kinase, readying this enzyme to phosphorylate other proteins.

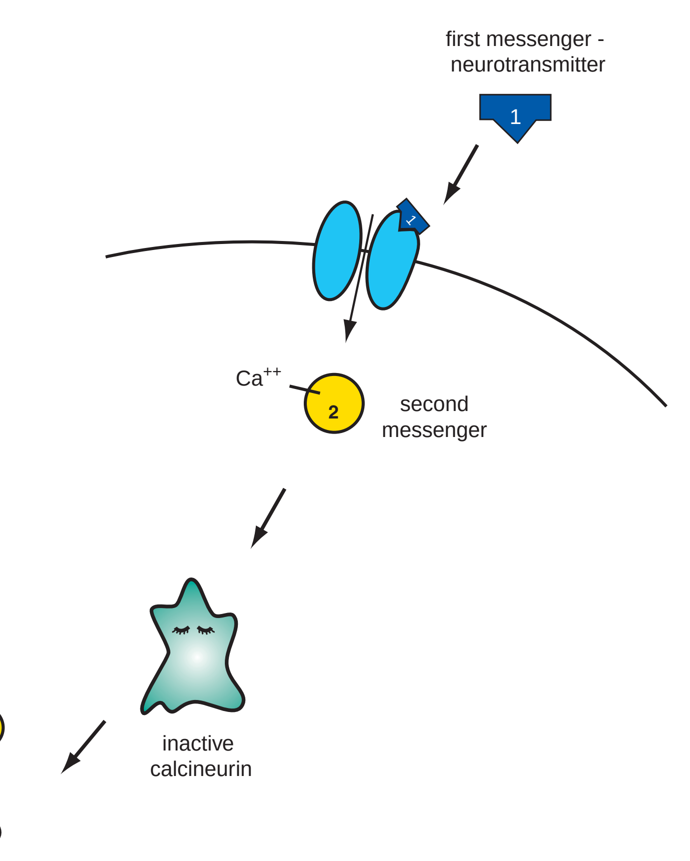


Figure 1-17. Third-messenger phosphatase. This figure illustrates activation of a third-messenger phosphatase through the second-messenger calcium. Shown here is calcium binding to an inactive phosphatase known as calcineurin, thereby activating it and thus readying it to remove phosphates from fourth-messenger phosphoproteins.

(Figure 1-17). In the case of kinase activation, two copies of the second messenger target each regulatory unit of dormant or "sleeping" protein kinase (Figure 1-16). When some protein kinases are inactive, they exist in dimers (two copies of the enzyme) while binding to a regulatory unit, thus rendering them in a conformation that is not active. In this example, when two copies of cAMP bind to each regulatory unit, the regulatory unit dissociates from the enzyme, the dimer dissociates into two copies of the enzyme, and the protein kinase is now activated, shown with bow and arrow ready to shoot phosphate groups into unsuspecting fourth-messenger phosphoproteins (Figure 1-16).

Meanwhile, the nemesis of protein kinase is also forming, namely a protein phosphatase (Figure 1-17). Another first messenger is opening an ion channel here, allowing second-messenger calcium to enter, which activates the phosphatase enzyme calcineurin. In the presence of calcium, calcineurin becomes activated, shown with scissor fingers ready to rip phosphate groups off fourth-messenger phosphoproteins (Figure 1-17).

The clash between kinase and phosphatase can be seen by comparing what happens in Figures 1-18 and 1-19. In Figure 1-18, third-messenger kinase is putting phosphates onto various fourth-messenger phosphoproteins such as ligand-gated ion channels, voltage-gated ion channels, and enzymes. In Figure 1-19, third-messenger phosphatase is taking those phosphates off. Sometimes phosphorylation activates a dormant phosphoprotein; for other phosphoproteins, dephosphorylation can be activating. Activation of fourth-messenger phosphoproteins can change the synthesis of neurotransmitters, alter neurotransmitter release, change the conductance of ions, and generally maintain the chemical neurotransmission apparatus in

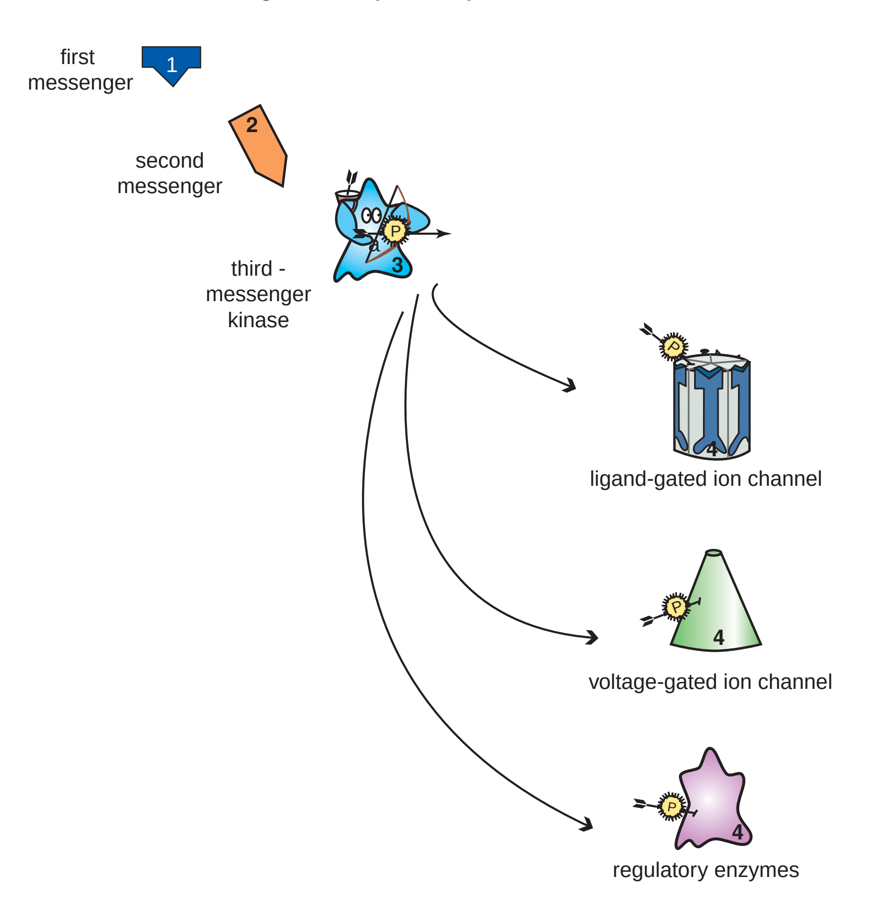


Figure 1-18. Third-messenger kinase puts phosphates on critical proteins. Here the activation of a third-messenger kinase adds phosphates to a variety of phosphoproteins, such as ligand-gated ion channels, voltage-gated ion channels, and various regulatory enzymes. Adding a phosphate group to some phosphoproteins activates them; for other proteins, this inactivates them.

either a state of readiness or dormancy. The balance between phosphorylation and dephosphorylation of fourth-messenger kinases and phosphatases plays a vital role in regulating many molecules critical to the chemical neurotransmission process.

Beyond the second messenger to a phosphoprotein cascade triggering gene expression

The ultimate cellular function that neurotransmission often seeks to modify is gene expression, either turning a gene on or turning a gene off. All four signal transduction cascades shown in Figure 1-11 end with the last molecule influencing gene transcription. Both cascades triggered by neurotransmitters are shown acting upon the CREB system, which is responsive to phosphorylation of its regulatory units (Figure 1-11 on the left). CREB is cAMP response element-binding protein, a transcription factor in the cell nucleus capable of activating expression of genes, especially a type of gene known as immediate genes or immediate early genes. When G-protein-linked receptors activate protein kinase A, this activated enzyme can translocate or move into the cell nucleus and stick a phosphate group on CREB, thus activating this transcription factor and causing the nearby gene to become activated. This leads to gene expression, first as RNA and then as the protein coded by the gene.

Interestingly, it is also possible for ion-channel-linked receptors that enhance intracellular second-messenger calcium levels to activate CREB by phosphorylating it. A protein known as calmodulin, which interacts with calcium, can lead to activation of certain kinases called calcium/calmodulin-dependent protein kinases (Figure 1-11). This is an entirely different enzyme than the phosphatase shown in Figures 1-9, 1-17 and 1-19. Here, a kinase and not a phosphatase is activated. When activated, this kinase can translocate into the

Third-Messenger Phosphatases Undo what Kinases Create - Take Phosphates Off Critical Proteins

first messenger - neurotransmitter
1
Ca++
2
second messenger
ligand-gated ion channel
4
P
voltage-gated ion channel
regulatory enzymes
inactive calcineurin
third messenger - active calcineurin (phosphatase)
3

Figure 1-19. Third-messenger phosphatase removes phosphates from critical proteins. In contrast to the previous figure, the third messenger here is a phosphatase; this enzyme removes phosphate groups from phosphoproteins such as ligand-gated ion channels, voltage-gated ion channels, and various regulatory enzymes. Removing a phosphate group from some phosphoproteins activates them; for others, it inactivates them.

cell nucleus and, just like the kinase activated by the G-protein system, add a phosphate group to CREB and activate this transcription factor so that gene expression is triggered.

It is important to bear in mind that calcium is thus able to activate both kinases and phosphatases. There is a very rich and sometimes confusing array of kinases and phosphatases, and the net result of calcium action is dependent upon what substrates are activated, because different phosphatases and kinases target very different substrates. Thus, it is important to keep in mind the specific signal transduction cascade under discussion, and the specific phosphoproteins acting as messengers in the cascade, in order to understand the net effect of various signal transduction cascades. In the case illustrated in Figure 1-11, the G-protein system and the ion-channel system are working together to produce more activated kinases and thus more activation of CREB. However, in Figures 1-9, and 1-16 through 1-19, they are working in opposition.

Genes are also the ultimate target of the hormone signal transduction cascade in Figure 1-11. Some hormones, such as estrogen, thyroid, and cortisol, act at cytoplasmic receptors, bind them, and produce a hormone–nuclear receptor complex that translocates to the cell nucleus, finds elements in the gene that it can influence (called hormone response elements, or HREs), and then acts as a transcription factor to trigger activation of nearby genes (Figure 1-11).

Finally, a very complicated signal transduction system with terrible-sounding names for their downstream signal cascade messengers is activated by neurotrophins and related molecules. Activating this system by first-messenger neurotrophins leads to activation of enzymes that are mostly kinases, one kinase activating another until finally one of them phosphorylates a transcription factor in the cell nucleus and starts transcribing genes (Figure 1-11). Ras is a G protein that activates a cascade of kinases with confusing names. For those who are good sports with an interest in the specifics, this cascade starts with Ras activating Raf, which phosphorylates and activates MEK (MAP kinase/ERK kinase, or mitogen-activated protein kinase/extracellular-signal-regulated kinase kinase), which activates ERK

(extracellular signal-regulated kinase itself), RSK (ribosomal S6 kinase), MAPK (MAP kinase itself), or GSK-3 (glycogen synthase kinase), leading ultimately to changes in gene expression. Confused? It is actually not important to know the names, but to remember the take-away point that neurotrophins trigger an important signal transduction pathway that activates kinase enzyme after kinase enzyme, ultimately changing gene expression. This is worth knowing, because this signal transduction pathway may be responsible for the expression of genes that regulate many critical functions of the neuron, such as synaptogensis and cell survival, as well as the plastic changes that are necessary for learning, memory, and even disease expression in various brain circuits. Both drugs and the environment target gene expression in ways that are just beginning to be understood, including how such actions contribute to the cause of mental illnesses and to the mechanism of action of effective treatments for mental illnesses.

In the meantime, it is mostly important to realize that a very wide variety of genes are targeted by all four of these signal transduction pathways. These range from the genes that make synthetic enzymes for neurotransmitters, to growth factors, cytoskeleton proteins, cellular adhesion proteins, ion channels, receptors, and the intracellular signaling proteins themselves, among many others. When genes are expressed by any of the signal transduction pathways shown in Figure 1-11, this can lead to making more or fewer copies of any of these proteins. Synthesis of such proteins is obviously a critical aspect of the neuron performing its many and varied functions. Numerous diverse biological actions are effected within neurons that alter behaviors in individuals due to gene expression that is triggered by the four major signal transduction cascades. These functions include synaptogensis, strengthening of a synapse, neurogenesis, apoptosis, increasing or decreasing the efficiency of information processing in cortical circuits, to behavioral responses such as learning, memory, antidepressant responses to antidepressant administration, symptom reduction by psychotherapy, and possibly even the production of a mental illness.

How neurotransmission triggers gene expression

How does the gene express the protein it codes? The discussion above has shown how the molecular "pony express" of signal transduction has a message encoded with chemical information from the neurotransmitter–receptor complex that is passed along from molecular rider to molecular rider until the message is delivered to the appropriate phosphoprotein mailbox (Figures 1-9 and 1-16 through 1-19) or DNA mailbox in the postsynaptic neuron's genome (Figures 1-11 and 1-20 through 1-30). Since the most powerful way for a neuron to alter its function is to change which genes are being turned on or off, it is important to understand the molecular mechanisms by which neurotransmission regulates gene expression.

How many potential genes can neurotransmission target? It is estimated that the human genome contains approximately *20 000 to 30 000 genes* located within *3 million base pairs* of DNA on 23 chromosomes. Incredibly, however, genes only occupy a few percent of this DNA. The other 97% used to be called "junk" DNA since it does not code proteins, but it is now known that these sections of DNA are critical for regulating whether or not a gene is expressed or is silent. It is not just the number of genes we have, it is whether, when, how often, and under what circumstances they are expressed that seems to be the important factor in regulating neuronal function. These same factors of gene expression are now thought to also underlie the actions of psychopharmacologic drugs and the mechanisms of psychiatric disorders within the central nervous system.

Molecular mechanism of gene expression

Chemical neurotransmission converts receptor occupancy by a neurotransmitter into the creation of third, fourth, and subsequent messengers that eventually activate transcription factors that turn on genes (Figures 1-20 through 1-30). Most genes have two regions, a *coding region* and a *regulatory region* with enhancers and promoters of gene transcription (Figure 1-20). The coding region is the direct template for making its corresponding RNA. This DNA can be transcribed into its RNA with the help of an enzyme called *RNA polymerase*. However, RNA polymerase must be activated or it won't work.

Luckily, the regulatory region of the gene can make this happen. It has an *enhancer element* and a *promoter element* (Figure 1-20), which can initiate gene expression with the help of transcription factors (Figure 1-21). Transcription factors themselves can be activated when they are phosphorylated, which allows them to bind to the regulatory region of the gene (Figure 1-21). This in turn activates RNA polymerase and off we go, with the coding part of the gene *transcribing* itself into its mRNA (Figure 1-22). Once

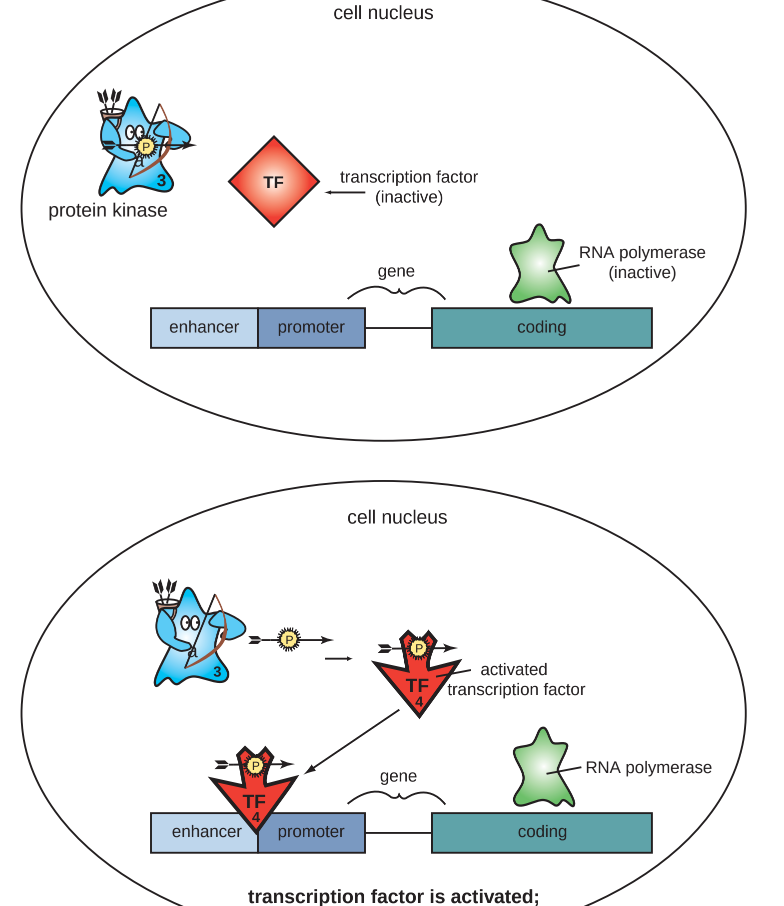


Figure 1-20. Activation of a gene, part 1: gene is off. The elements of gene activation shown here include the enzyme protein kinase; a transcription factor, a type of protein that can activate a gene; RNA polymerase, the enzyme that synthesizes RNA from DNA when the gene is transcribed; the regulatory regions of DNA, such as enhancer and promoter areas; and finally the gene itself. This particular gene is off because the transcription factor has not yet been activated. The DNA for this gene contains both a regulatory region and a coding region. The regulatory region has both an enhancer element and a promoter element, which can initiate gene expression when they interact with activated transcription factors. The coding region is directly transcribed into its corresponding RNA once the gene is activated.

Figure 1-21. Activation of a gene, part 2: gene turns on. The transcription factor is now activated because it has been phosphorylated by protein kinase, allowing it to bind to the regulatory region of the gene.

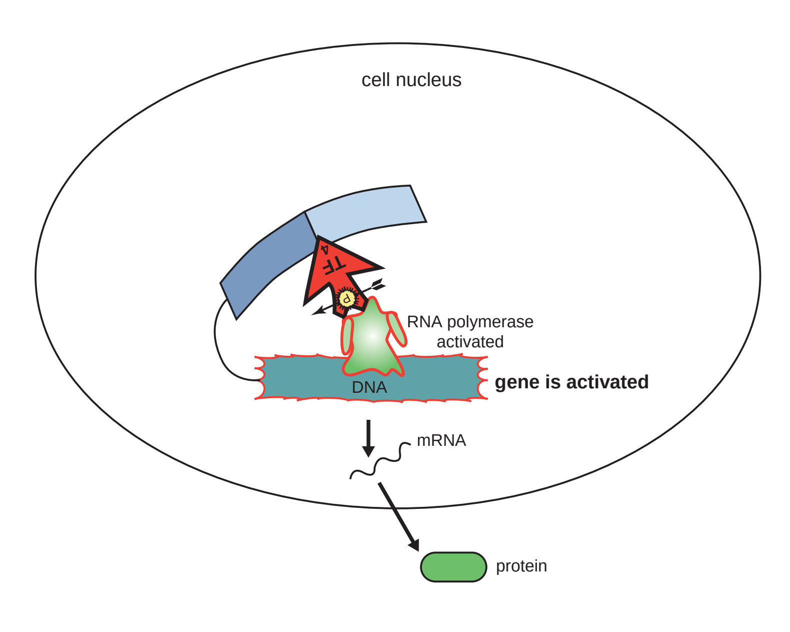


Figure 1-22. Activation of a gene, part 3: gene product. The gene itself is now activated because the transcription factor has bound to the regulatory region of the gene, in turn activating the enzyme RNA polymerase. The gene is transcribed into messenger RNA (mRNA), which in turn is translated into its corresponding protein. This protein is thus the product of activation of this particular gene.

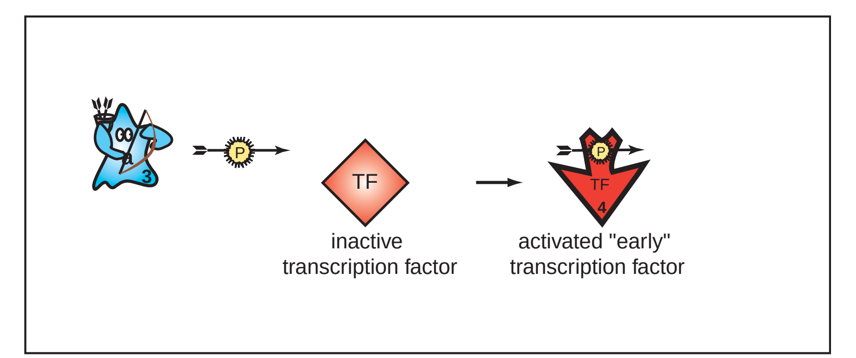
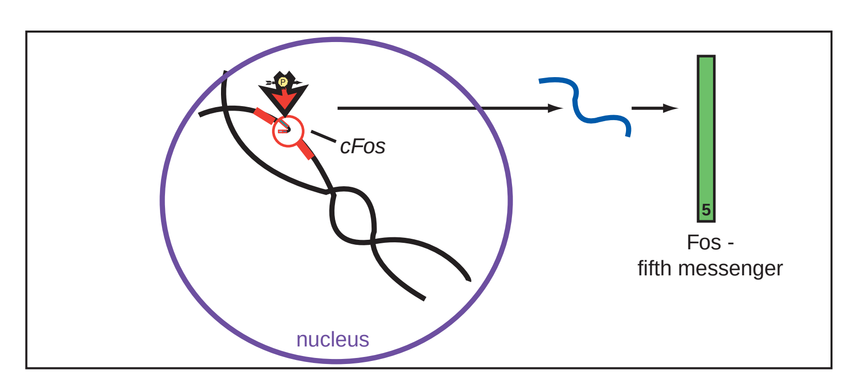


Figure 1-23. Immediate early gene. Some genes are known as immediate early genes. Shown here is a third-messenger protein kinase enzyme activating a transcription factor, or fourth messenger, capable of activating, in turn, an early gene.



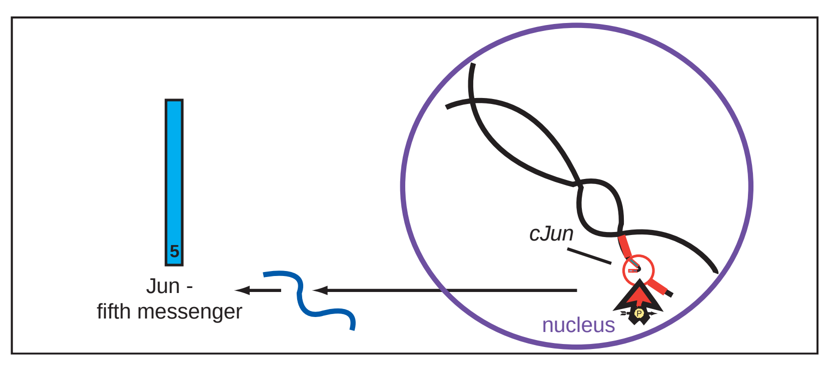


Figure 1-24. Early genes activate late genes, part 1. In the top panel, a transcription factor is activating the immediate early gene *cFos* and producing the protein product Fos. While the *cFos* gene is being activated, another immediate early gene, *cJun*, is being simultaneously activated and producing its protein, Jun, as shown in the bottom panel. Fos and Jun can be thought of as fifth messengers.

transcribed, of course, the RNA goes on to *translate* itself into the corresponding protein (Figure 1-22).

Some genes are known as immediate early genes (Figure 1-23). They have weird names such as *cJun* and *cFos* (Figures 1-24 and 1-25) and belong to a family called "leucine zippers" (Figure 1-25). These immediate early genes function as rapid responders to the neurotransmitter's input, like the special ops troops sent into combat quickly and ahead of the full army. Such rapid-deployment forces of immediate early genes are thus the first to respond to the neurotransmission signal by making the proteins they encode. In this example, it is Jun and Fos proteins coming from *cJun* and *cFos* genes (Figure 1-24). These are nuclear proteins; that is, they live and work in the nucleus. They get started within 15 minutes of receiving a neurotransmission but last for only a half hour to an hour (Figure 1-10).

When Jun and Fos team up, they form a leucine zipper type of transcription factor (Figure 1-25), which in turn activates many kinds of later-onset genes

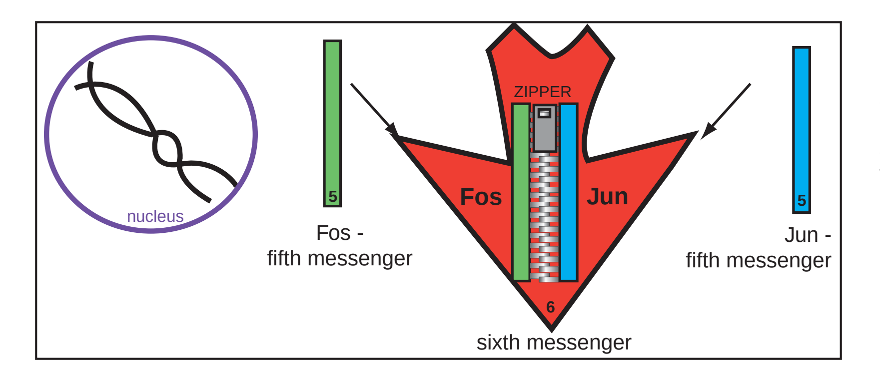


Figure 1-25. Early genes activate late genes, part 2. Once Fos and Jun proteins are synthesized, they can collaborate as partners and produce a Fos-Jun combination protein, which now acts as a sixth-messenger transcription factor for late genes.

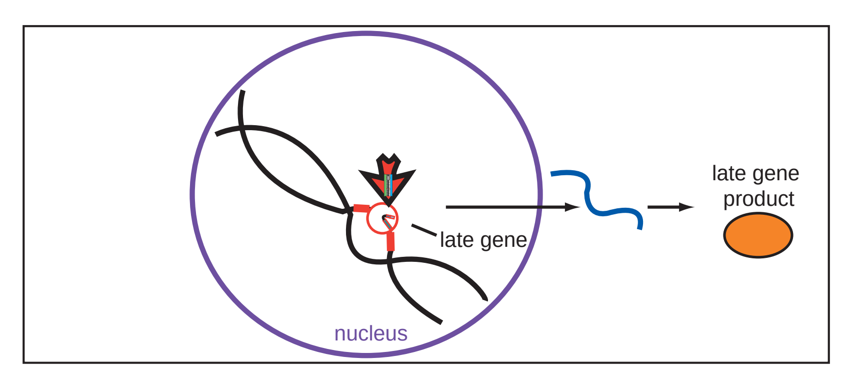


Figure 1-26. Early genes activate late genes, part 3. The Fos-Jun transcription factor belongs to a family of proteins called leucine zippers. The leucine zipper transcription factor formed by the products of the activated early genes *cFos* and *cJun* now returns to the genome and finds another gene. Since this gene is being activated later than the others, it is called a late gene. Thus, early genes activate late genes when the products of early genes are themselves transcription factors. The product of the late gene can be any protein the neuron needs, such as an enzyme, a transport factor, or a growth factor.

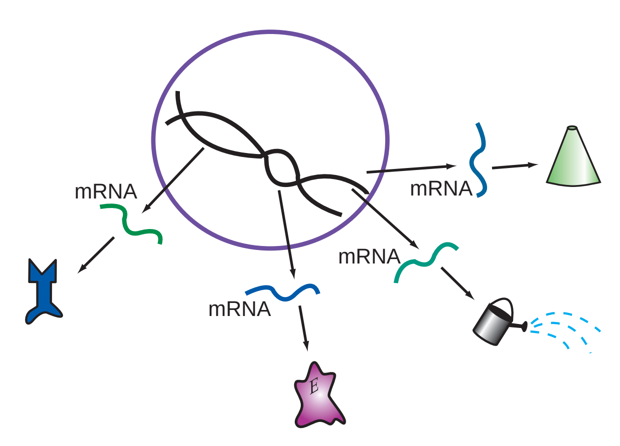


Figure 1-27. Examples of late gene activation. A receptor, an enzyme, a neurotrophic growth factor, and an ion channel are all being expressed owing to activation of their respective genes. Such gene products go on to modify neuronal function for many hours or days.

(Figures 1-26, 1-27, 1-29). Thus, Jun and Fos serve to wake up the much larger army of inactive genes. Which individual "late" soldier genes are so drafted to active gene duty depends upon a number of factors, not the least of which is which neurotransmitter is sending the message, how frequently it is sending the message, and whether it is working in concert or in opposition with other neurotransmitters talking to other parts of the same neuron at the same time. When Jun and Fos partner together to form a leucine zipper type of transcription factor, this can lead to the activation of genes to make anything you can think of, from enzymes to receptors to structural proteins (Figure 1-27).

In summary, one can trace the events from neurotransmitting first messenger through gene transcription (Figures 1-9, 1-11, 1-28, 1-29). Once the second-messenger cAMP is formed from its first-messenger neurotransmitter (Figure 1-28), it can interact with a protein kinase third messenger. cAMP binds to the inactive or sleeping version of this enzyme, wakes it up, and thereby activates protein kinase. Once awakened, the protein kinase third messenger's job is to activate transcription factors by phosphorylating them (Figure 1-28). It does this by traveling straight to the cell nucleus and finding a sleeping transcription factor. By sticking a phosphate onto the transcription factor, protein kinase is able to "wake up" that transcription factor and form a fourth messenger (Figure 1-28). Once a transcription factor is aroused, it will bind to genes and cause protein

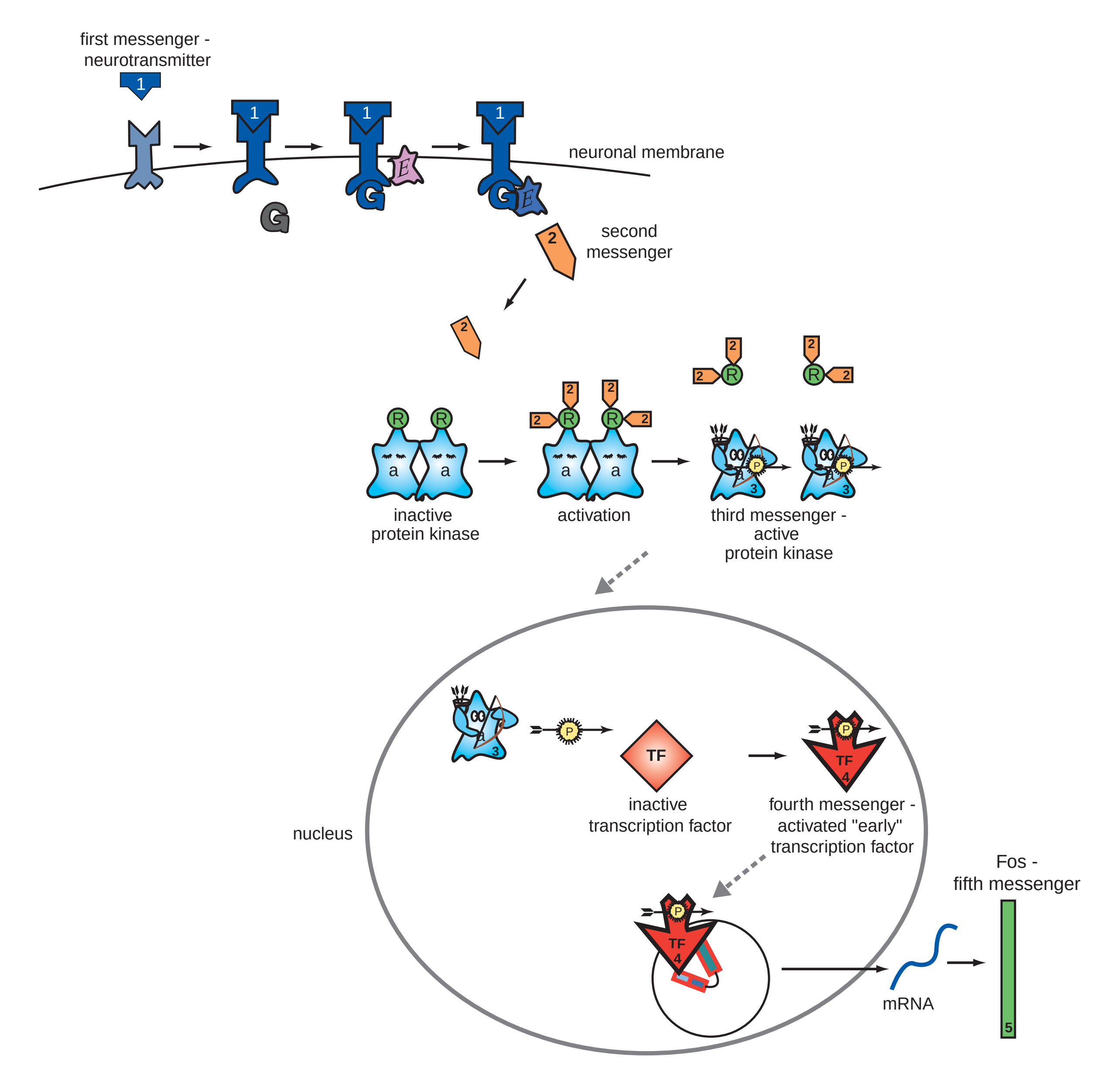


Figure 1-28. Gene regulation by neurotransmitters. This figure summarizes gene regulation by neurotransmitters, from first-messenger extracellular neurotransmitter to intracellular second messenger, to third-messenger protein kinase, to fourth-messenger transcription factor, to fifth-messenger protein, which is the gene product of an early gene.

synthesis; in this case, the product of an immediate early gene, which functions as a fifth messenger. Two such gene products bind together to form yet another activated transcription factor, and this is the sixth messenger (Figure 1-29). Finally, the sixth messenger causes the expression of a late gene product, which could be thought of as a seventh-messenger protein product of the activated gene. This late gene product then mediates some biological response important to the functioning of the neuron.

Of course, neurotransmitter-induced molecular cascades into the cell nucleus lead to changes not only in the synthesis of its own receptors but also in that of many other important postsynaptic proteins, including enzymes and receptors for other neurotransmitters. If such changes in genetic expression lead to changes

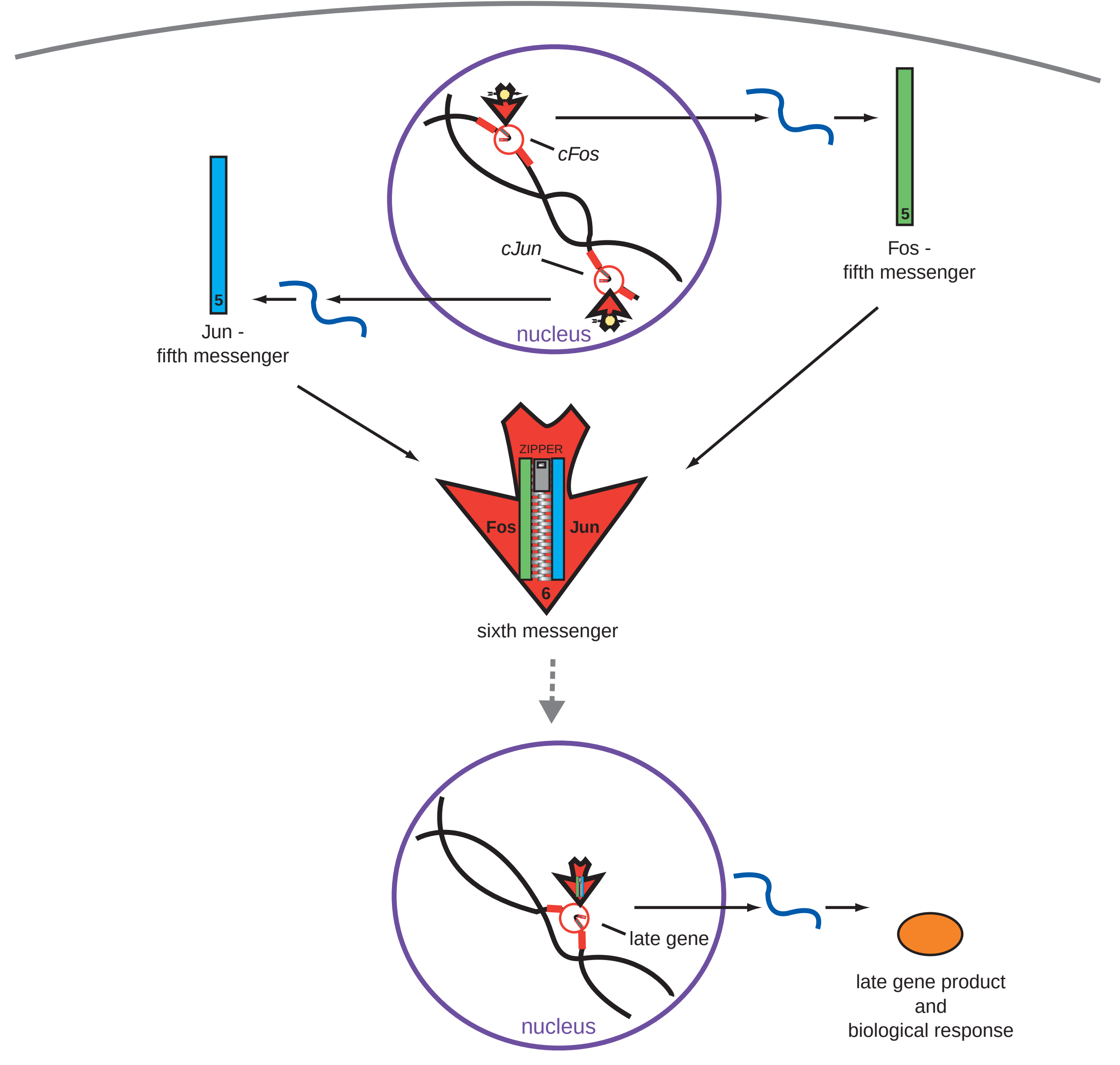


Figure 1-29. Activating a late gene. This figure summarizes the process of activating a late gene. At the top, immediate early genes *cFos* and *cJun* are expressed and their fifth-messenger protein products Fos and Jun are formed. Next, a transcription factor, namely a leucine zipper, is created by the cooperation of Fos and Jun together, combining to form the sixth messenger. Finally, this transcription factor goes on to activate a late gene, resulting in the expression of its own gene product and the biological response triggered by that late gene product.

in connections and in the functions that these connections perform, it is easy to understand how genes can *modify behavior*. The details of nerve functioning – and thus the behavior derived from this nerve functioning – are controlled by genes and the products they produce. Since mental processes and the behaviors they cause come from the connections between neurons in the brain, genes therefore exert significant control over behavior. But can behavior modify genes? Learning as well as experiences from the environment can indeed alter which genes are expressed and thus can give rise to changes in neuronal connections. In this way, human experiences, education, and even psychotherapy may change the expression of genes that alter the distribution and "strength" of specific synaptic connections. This in turn may produce long-term changes in behavior caused by the original experience and mediated by the genetic changes triggered by that original experience.

Thus, genes modify behavior and behavior modifies genes. Genes do not directly regulate neuronal functioning. Rather, they directly regulate the proteins that create neuronal functioning. Changes in function have to wait until the changes in protein synthesis occur and the events they cause start to happen.

Epigenetics

Genetics is the DNA code for what a cell can transcribe into specific types of RNA or translate into specific proteins. However, just because there are over 20 000 genes in the human genome, it does not mean that every gene is expressed, even in the brain. Epigenetics is a parallel system that determines whether any given gene is actually made into its specific RNA and protein, or if it is instead ignored or silenced. If the genome is a lexicon of all protein "words," then the epigenome is a "story" resulting from arranging the "words" into a coherent tale. The genomic lexicon of all potential proteins is the same in every one of the 10+ billion neurons in the brain, and indeed is the same in all of the 200+ types of cells in the body. So, the plot of how a normal neuron becomes a malfunctioning neuron in a psychiatric disorder, as well as how a neuron becomes a neuron instead of a liver cell, is the selection of which specific genes are expressed or silenced. In addition, malfunctioning neurons are impacted by inherited genes that have abnormal nucleotide sequences, which if expressed contribute to mental disorders. Thus, the story of the brain depends not only on which genes are inherited but also on whether any abnormal genes are expressed or even whether normal genes are expressed when they should be silent or silenced when they should be expressed. Neurotransmission, genes themselves, drugs, and the environment all regulate which genes are expressed or silenced, and thus all affect whether the story of the brain is a compelling narrative such as learning and memory, a regrettable tragedy such as drug abuse, stress reactions, and psychiatric disorders, or therapeutic improvement of a psychiatric disorder by medications or psychotherapy.

What are the molecular mechanisms of epigenetics?

Epigenetic mechanisms turn genes on and off by modifying the structure of chromatin in the cell nucleus (Figure 1-30). The character of a cell is fundamentally determined by its chromatin, a substance composed of nucleosomes (Figure 1-30). Nucleosomes are an octet of proteins called histones around which DNA is wrapped (Figure 1-30). Epigenetic control over whether a gene is read (i.e., expressed) or is not read (i.e., silenced), is achieved by modifying the structure of chromatin. Chemical modifications that can do this include not only methylation, but also acetylation, phosphorylation, and other processes that are regulated by neurotransmission, drugs, and the environment (Figure 1-30). For example, when DNA or histones are methylated, this compacts the chromatin and acts to close off access of molecular transcription factors to the promoter regions of DNA, with the consequence that the gene in this region is silenced, and not expressed, so no RNA or protein is manufactured (Figure 1-30). Silenced DNA means molecular features that are not part of a given cell's personality.

Histones are methylated by enzymes called histone methyl-transferases, and this is reversed by enzymes called histone demethylases (Figure 1-30). Methylation of histones can silence genes, whereas demethylation of histones can activate genes. DNA can also be methylated, and this also silences genes. Demethylation of DNA reverses this. Methylation of DNA is regulated by DNA methyl-transferase (DNMT) enzymes, and demethylation of DNA by DNA demethylase enzymes (Figure 1-30). There are many forms of methyl-transferase enzymes, and they all tag their substrates with methyl groups donated from L-methylfolate via S-adenosyl-methionine (SAMe) (Figure 1-30). When neurotransmission, drugs, or the environment affect methylation, this regulates whether genes are epigenetically silenced or expressed.

Methylation of DNA can eventually lead to deacetylation of histones as well, by activating enzymes called histone deacetylases (HDACs). Deacetylation of histones also has a silencing action on gene expression (Figure 1-30). Methylation and deacetylation compress chromatin, as though a molecular gate has been closed. This prevents transcription factors from accessing the promoter regions that activate genes; thus, the genes are silenced and not transcribed into RNA or translated into proteins (Figure 1-30). On the other hand, demethylation and acetylation do just the oppostite: they decompress chromatin as though a molecular gate has been opened, and thus transcription factors can get to the promoter regions of genes and activate them (Figure 1-30). Activated genes thus become part of the molecular personality of a given cell.

Gene Activation and Silencing

Gene Activating
histone acetyl transferase
DNA demethylase
histone demethylase

Ac
gates open
TF
Ac

neurotransmission/
drugs/
environment

Me
TF
Me
gates close

mRNA

gene product

activated gene

Gene Silencing
histone deacetylase
DNMT
histone methyl-transferase

DNMT
Me
SAMe
CH_3
H H
L-MF
H H

mRNA

gene product

silenced gene

Key

TF
transcription factor

chromatin (histone + DNA)

Me Me Me Me
methylated DNA

CH_3
H H
L-MF
H H
L-methylfolate

Me
methylated histone core

Me
methyl group

Ac
acetyl group

Figure 1-30. Gene activation and silencing. Molecular gates are opened by acetylation and/or demethylation of histones, allowing transcription factors access to genes, thus activating them. Molecular gates are closed by deacetylation and/or methylation provided by the methyl donor SAMe derived from L-methylfolate. This prevents access of transcription factors to genes, thus silencing them. Ac, acetyl; Me, methyl; DNMT, DNA methyl-transferase; TF, transcription factor; SAMe, S-adenosyl-methionine; L-MF, L-methylfolate.

How epigenetics maintains or changes the status quo

Some enzymes try to maintain the status quo of a cell, such as DNMT1 (DNA methyl-transferase 1), which maintains the methylation of specific areas of DNA and keeps various genes quiet for a lifetime. That is, this process keeps a neuron a neuron and a liver cell a liver cell, including when a cell divides into another one. Presumably, methylation is maintained at genes that one cell does not need, even though another cell type might.

It used to be thought that, once a cell differentiated, the epigenetic pattern of gene activation and gene silencing remained stable for the lifetime of that cell. Now, however, it is known that there are various circumstances in which epigenetics may change in mature, differentiated neurons. Although the initial epigenetic pattern of a neuron is indeed set during neurodevelopment to give each neuron its own lifelong "personality," it now appears that the storyline of some neurons is that they respond to their narrative experiences throughout life with a changing character arc, thus causing de novo alterations in their epigenome. Depending upon what happens to a neuron (such as child abuse, adult stress, dietary deficiencies, productive new encounters, psychotherapy, drugs of abuse, or psychotropic therapeutic medications), it now seems that previously silenced genes can become activated and/or previously active genes can become silenced (Figure 1-30). When this happens, both favorable and unfavorable developments can occur in the character of neurons. Favorable epigenetic mechanisms may be triggered in order for one to learn (e.g., spatial memory formation) or to experience the therapeutic actions of psychopharmacologic agents. On the other hand, unfavorable epigenetic mechanisms may be triggered in order for one to become addicted to drugs of abuse or to experience various forms of "abnormal learning," such as when one develops fear conditioning, an anxiety disorder, or a chronic pain condition.

How these epigenetic mechanisms arrive at the scene of the crime remains a compelling neurobiological and psychiatric mystery. Nevertheless, a legion of scientific detectives is working on these cases and is beginning to show how epigenetic mechanisms are mediators of psychiatric disorders. There is also the possibility that epigenetic mechanisms can be harnessed to treat addictions, extinguish fear, and prevent the development of chronic pain states. It may even be possible to prevent disease progression of psychiatric disorders such as schizophrenia by identifying high-risk individuals before the "plot thickens" and the disorder is irreversibly established and relentlessly marches on to an unwanted destiny.

One of the mechanisms for changing the status quo of epigenomic patterns in a mature cell is via de novo DNA methylation by a type of DNMT enzyme known as DNMT2 or DNMT3 (Figure 1-30). These enzymes target neuronal genes for silencing that were previously active in a mature neuron. Of course, deacetylation of histones near previously active genes would do the same thing, namely silence them, and this is mediated by the enzymes called histone deacetylases (HDACs). In reverse, demethylation or acetylation both activate genes that were previously silent. The real question is, how does a neuron know which genes among its thousands to silence or activate in response to the environment, including stress, drugs, and diet? How might this go wrong when a psychiatric disorder develops? This part of the story remains a twisted mystery, but some very interesting detective work has already been done by various investigators who hope to understand how some neuronal stories evolve into psychiatric tragedies. These investigations may set the stage for rewriting the narrative of various psychiatric disorders by therapeutically altering the epigenetics of key neuronal characters so that the story has a happy ending.

Summary

The reader should now appreciate that chemical neurotransmission is the foundation of psychopharmacology. There are many neurotransmitters, and all neurons receive input from a multitude of neurotransmitters in classic presynaptic to postsynaptic asymmetrical neurotransmission. Presynaptic to postsynaptic neurotransmissions at the brain's trillion synapses are key to chemical neurotransmission, but some neurotransmission is retrograde from postsynaptic neuron to presynaptic neuron, and other types of neurotransmission, such as volume neurotransmission, do not require a synapse at all.

The reader should also have an appreciation for elegant if complex molecular cascades precipitated by a neurotransmitter, with molecule-by-molecule transfer of the transmitted message inside the neuron receiving that message, eventually altering

the biochemical machinery of that cell in order to act upon the message that was sent to it. Thus, the function of chemical neurotransmission is not so much to have a presynaptic neurotransmitter communicate with its postsynaptic receptors, but to have a *presynaptic genome converse with a postsynaptic genome*: DNA to DNA, presynaptic "command center" to postsynaptic "command center" and back.

The message of chemical neurotransmission is transferred via three sequential "molecular pony express" routes: (1) a presynaptic neurotransmitter synthesis route from presynaptic genome to the synthesis and packaging of neurotransmitter and supporting enzymes and receptors; (2) a postsynaptic route from receptor occupancy through second messengers all the way to the genome, which turns on postsynaptic genes; and (3) another postsynaptic route starting from the newly expressed postsynaptic genes transferring information as a molecular cascade of biochemical consequences throughout the postsynaptic neuron.

It should now be clear that neurotransmission does not end when a neurotransmitter binds to a receptor, or even when ion flows have been altered or second messengers have been created. Events such as these all start and end within milliseconds to seconds following release of presynaptic neurotransmitter. The ultimate goal of neurotransmission is to alter the biochemical activities of the postsynaptic target neuron in a profound and enduring manner. Since the postsynaptic DNA has to wait until molecular pony express messengers make their way from the postsynaptic receptors, often located on dendrites, to phosphoproteins within the neuron, or to transcription factors and genes in the postsynaptic neuron's cell nucleus, it can take a while for neurotransmission to begin influencing the postsynaptic target neuron's biochemical processes. The time it takes from receptor occupancy by neurotransmitter to gene expression is usually hours. Furthermore, since the last messenger triggered by neurotransmission – called a transcription factor – only initiates the very beginning of gene action, it takes even longer for the gene activation to be fully implemented via the series of biochemical events it triggers. These biochemical events can begin many hours to days after the neurotransmission occurred, and can last days or weeks once they are put in motion.

Thus, a brief puff of chemical neurotransmission from a presynaptic neuron can trigger a profound postsynaptic reaction that takes hours to days to develop and that can last days to weeks or even a lifetime. Every conceivable component of this entire process of chemical neurotransmission is a candidate for modification by drugs. Most psychotropic drugs act upon the processes that control chemical neurotransmission at the level of the neurotransmitters themselves, their enzymes, and especially their receptors. Future psychotropic drugs will undoubtedly act directly upon the biochemical cascades, particularly upon those elements that control the expression of pre- and postsynaptic genes. Also, mental and neurological illnesses are known or suspected to affect these same aspects of chemical neurotransmission. The neuron is dynamically modifying its synaptic connections throughout its life, in response to learning, life experiences, genetic programming, epigenetic changes, drugs, and diseases, with chemical neurotransmission being the key aspect underlying the regulation of all these important processes.